Total Synthesis of Spirofungins A and B and Formal Synthesis of the C1-C38 Fragment of (+)-Sorangicin A

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A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry.

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ABSTRACT

Elizabeth Anne O'Bryan: Total Synthesis of Spirofungins A and B and Formal Synthesis of the C1-C38 Fragment of (+)-Sorangicin A
(Under the direction of Michael T. Crimmins)

The enantioselective total synthesis of spirofungins A and B is reported in 14 steps over the longest linear sequence. The synthesis of three key fragments in six steps or less and excellent overall yield allowed for the assembly of spirofungins A and B in a highly efficient manner. Highlights of the synthesis include the use of thiazolidinethione-mediated aldol reactions to install five of the seven stereocenters, and the appendage of the C1-C6 unsaturated side chain through a challenging cross metathesis reaction.

Efforts towards the total synthesis of (+)-sorangicin A resulted in the completion of a formal synthesis of the C1-C38 fragment. The preparation of three orthogonally differentiated cyclic ether fragments allowed for the investigation of several coupling strategies for assembly of the natural product. A cross metathesis reaction was employed to form the C29-C30 bond and unite the bicyclic ether and tetrahydropyran fragments. It was our intention to utilize a second cross metathesis reaction to install the C15-C16 olefin and append the dihydropyran moiety to the rest of the molecule; however, a low yield for this cross metathesis reaction prompted us to instead use a Julia-Kocienski olefination to arrive at the C1-C38 fragment. Completion of the total synthesis of (+)-sorangicin A can be achieved in six known steps from this advanced intermediate.
ACKNOWLEDGEMENTS

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Finally, I must thank my family for being there through the many ups and downs of my graduate career. I am lucky to have such a wonderful support system, not only
from my parents, but also my siblings- Andy, Mitchell, Tom, and Will. I know I can always count on my brothers to brighten my mood just by being the fun and supportive people that they are. I have learned so much from them, in particular Mitchell, whose strength and loving spirit throughout his life continues to be a source of inspiration for all of us.

I certainly could not have reached this point without the positive example of family, faith, and hard work provided by my parents. The values they have instilled in me have helped guide me through the challenges that come with graduate school. Thank you for helping me celebrate my accomplishments and for always being excited about my work. I cannot begin to express how thankful I am for your never-ending patience, love, and support for everything that I do.
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<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>Azobis(isobutynitrile)</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl (substituted aryl ring)</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlation spectroscopy</td>
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<tr>
<td>CSA</td>
<td>Camphorsulfonic acid</td>
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<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
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<td>DIAD</td>
<td>Diisopropylazadicarboxylate</td>
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<td>DBU</td>
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<tr>
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<td>Grubbs’ 1&lt;sup&gt;st&lt;/sup&gt; generation catalyst</td>
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<tr>
<td>HMDS</td>
<td>Hexamethyldisilazide</td>
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</tr>
<tr>
<td>Piv</td>
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</tr>
<tr>
<td>TPAP</td>
<td>Tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>Trisyl</td>
<td>2,4,6-Triisopropylbenzenesulfonyle</td>
</tr>
<tr>
<td>Ts</td>
<td>para-Toluenesulfonyle</td>
</tr>
</tbody>
</table>
CHAPTER ONE

Background: Spirofungins A and B

1.1 Isolation, structural assignment, and biological activity

Spiroketal-containing natural products are abundant in nature and have been isolated as secondary metabolites from a number of insects, fungi, plants, and marine organisms. The increasing pharmacological importance of these naturally-occurring molecules has stimulated intense interest from the chemical community with regard to both their synthesis and chemical reactivity. For several years, our group has been interested in the synthesis of spiroketals due to their diverse biological profiles and complex architectures. As such, the spirofungins were identified as ideal targets for total synthesis as they possess several synthetically challenging features and important biological properties.

Spirofungins A (1) and B (2) were isolated by Höltzel and co-workers in 1998 as secondary metabolites of *Streptomyces violaceosiniger* Tü 4113 as a 4:1 mixture.¹ The spirofungins are closely related to the reveromycins,²,³ specifically reveromycin A (4), which possesses a similar 6,6-spiroketal core (Figure 1.1).² The spiroketal core for both the spirofungins and reveromycin A is flanked on both sides by identical C1-C10 and C20-C24 unsaturated acid side chains. The key difference between these natural
products is in the substitution at C18, in which reveromycin A possesses a hemisuccinate and \( n \)-butyl chain, while the spirofungins have a methyl group at this position.

![Structural formulas of spirofungins and reveromycin](image)

**Figure 1.1.** Spirofungins A and B and Reveromycin A.

Structural elucidation of spirofungins A and B was carried out primarily by utilizing various NMR techniques. Although a slight difference in retention time between spirofungin A and B was observed upon analysis by reverse phase HPLC, determination of the structure was carried out on the mixture.\(^1\) Spirofungin B was originally assigned as the C18 and C19 epimer (3) of the major component, spirofungin A (1). In 2004, Rizzacasa and co-workers completed the synthesis of the proposed structure of spirofungin B (3).\(^4\) Unfortunately, the spectral data for the synthetically prepared spirofungin B did not match what had been reported in the original isolation paper. Strong literature evidence led to the reassignment of spirofungin B (2) as the C15 epimer of spirofungin A. The structure and absolute stereochemistry of both spirofungin A and B were confirmed by total synthesis by Shimizu in 2005.\(^5\)

Spirofungin A, like the structurally related reveromycin A, has emerged as a popular target for synthesis due to its significant biological activity. The spirofungins
have been shown to possess high antifungal activity against yeasts, and moderate activity against filamentous fungi.\textsuperscript{1} Cell-based biological assays conducted on the mixture of spirofungins A and B determined the minimal inhibition concentration (MIC) to be 15 \( \mu \)g/mL for the human pathogen \textit{Candida albicans}. The Kozmin group recently demonstrated that spirofungin A suppresses the growth of several human cancer cell lines, including HL-60 (leukemia), HCT116 (colon), PC3 (prostate), and A549 (lung), with IC\textsubscript{50} values ranging from 0.64-6.4 \( \mu \)M.\textsuperscript{6} They also determined that spirofungin A selectively inhibits isoleucyl-tRNA synthetase in a dose dependent fashion. The biological profile of spirofungin A is consistent with the behavior of reveromycin A, which exhibits similar antifungal, antiproliferative, and inhibitory activity towards isoleucyl-tRNA synthetase.\textsuperscript{7-9} The mode of action for spirofungin A has yet to be determined, however, it has been suggested that it may be the same as the reveromycins, which inhibit protein synthesis in eukaryotic cells.

1.2 \textbf{Spirofungins and the anomeric effect}

A major challenge that is often encountered in the synthesis of spiroketal-containing natural products is formation of the spirocenter in a stereoselective fashion. A traditional approach to spiroketals, specifically the 6,6-spiroketals that make up the core of the spirofungins, involves acid-catalyzed condensation of a 1,9-dihydroxy ket-5-one (Figure 1.2). The stereochemical outcome of the spiroketalization event is influenced by a number of factors, including solvent, steric interactions, hydrogen bonding, and the anomeric effect.\textsuperscript{10,11}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{spiroketal.png}
\caption{Acid catalyzed formation of 6,6-spiroketal.}
\end{figure}
The anomeric effect was first observed by Edward in 1955 in the course of his work with pyranose sugars, and has since been extended to a wide range of cyclic and linear systems. In relation to the spiroketal systems of interest, the anomeric effect is defined as the preference for an electronegative substituent at the anomeric carbon (C2) to occupy the axial orientation as opposed to the sterically less demanding equatorial orientation. This is illustrated by 2-methoxytetrahydropyran, in which the axial configuration is favored in an 80:20 ratio (Figure 1.3).

![Diagram](image)

**Figure 1.3.** Conformation of 2-methoxytetrahydrofuran.

It has been proposed that the anomeric effect is the result of two contributing factors, a stabilizing molecular orbital overlap and a net dipole minimization. From a molecular orbital perspective, the anomeric effect is believed to arise from the overlap of the axial lone pair on the endocyclic oxygen with the antibonding $\sigma^*$ orbital of the exocyclic C-O bond (Figure 1.4). This stabilizing interaction is only possible when the C-O bond is anti-periplanar to the non-bonding oxygen lone pairs, resulting in delocalization of the lone pair of electrons and a decrease in the overall energy of the system.

![Diagram](image)

**Figure 1.4.** Molecule orbital rationalization for the anomeric effect.
The anomeric effect can also be rationalized in terms of a dipole minimization argument (Figure 1.5). The neighboring electronegative atoms result in a local dipole moment with a fixed orientation. When the electronegative substituent at the anomeric carbon is in an equatorial orientation there will be a dipole-dipole repulsion; however, in the axial orientation, the dipole-dipole interaction and the overall energy of the molecule are minimized.

![Figure 1.5. Dipole-dipole interaction as rationale for the anomeric effect.](image)

The contribution of the anomeric effect to overall energy has been estimated to provide approximately 1.4-2.4 kcal/mol stabilization, depending on the specific substrate. Consideration of the 6,6-spiroketal system reveals that there are four possible anomers that could be obtained upon acid-catalyzed spiroketalization of a generic dihydroxyketone (Figure 1.6). Without complication from other factors, A is the preferred conformation, in which the anti-periplanar relationship is realized for both oxygens.\(^{10,11,14}\)

![Figure 1.6. Conformation of 6,6-spiroketals.](image)

In spiroketal-containing natural products, such as the spirofungins, steric interactions and intramolecular hydrogen bonding, among other factors, can reinforce or
counteract the stabilization gained by the anomeric effect. Thus, the most stable spiroketal conformation is described as that in which the number of anomeric stabilizations is maximized, and unfavorable steric interactions are minimized.\(^\text{14}\)

Evaluation of spirofungins A and B reveals that spirofungin A possesses two anomeric stabilizations, while spirofungin B has a single anomeric stabilization (Figure 1.7). Despite the stabilization gained by the anomeric effect in spirofungin A, an undesirable steric interaction as a result of the axially oriented C20-C24 side chain causes the spirofungins to be very close in energy. Interestingly, the initially proposed structure of spirofungin B would be the most stable, since it is doubly anomeric and lacks the steric congestion caused by the C20-C24 side chain in spirofungin A.\(^\text{15}\)

![Figure 1.7. Chair conformations of the spirofungins.](image)

The minimal energy difference between the spirofungins makes the stereoselective synthesis of either spirofungin A or B a significant challenge. As will become evident from the synthetic efforts towards these natural products, subtle changes in the spiroketal precursor can have a marked effect on the selectivity of the spiroketalization.
1.3 Previous synthetic efforts

Due to the unique structure and important biological activity of the spirofungins, there has been considerable interest from the synthetic community in these natural products. Approaches toward the 6,6-spiroketal core have been reported by Kiyota,\textsuperscript{16} Dias,\textsuperscript{17,18} Rychnovsky,\textsuperscript{19} and most recently, Maier.\textsuperscript{20} Most of the aforementioned syntheses of the core feature an acid catalyzed spiroketalization to give rise to a mixture of spiroketal cores. Conversely, Rychnovsky and co-workers have developed a route for the selective preparation of the spirofungin B core which employs a highly efficient and stereoselective reductive cyclization.\textsuperscript{19} Total syntheses, which will be discussed herein, have been completed by the groups of Shimizu,\textsuperscript{5} Kozmin,\textsuperscript{6} and Rizzacasa,\textsuperscript{15} in addition to our own.\textsuperscript{21}

\textit{i. Shimizu’s synthesis of spirofungins A and B}

The Shimizu group achieved the first asymmetric total synthesis of spirofungins A and B in 2005.\textsuperscript{5} This group was also responsible for the first total synthesis of reveromycin A,\textsuperscript{22} and has recently reported the synthesis and biological evaluation of a series of reveromycin A and spirofungin A derivatives.\textsuperscript{23,24} Their approach towards the spirofungins takes advantage of the minimal energy difference, allowing for the preparation of both spirofungins A and B from a common intermediate. Their synthetic plan involved preparation of three key intermediates: alkyne 10, Weinreb amide 11, and vinyl boronate 5, from common intermediate 12 (Scheme 1.1).\textsuperscript{16,25} Retrosynthetically, they envisioned constructing spiroketal cores 7 (15\textsubscript{S}) and 8 (15\textsubscript{R}) by an acid-catalyzed spiroketalization of ynoate 9. Appendage of the C20-C24 and C1-C6 unsaturated side chains to the spiroketal core would be achieved by a Horner-Wadsworth-Emmons olefination with phosphonate 6 and a Suzuki coupling with vinyl boronate 5, respectively.
Common intermediate 12, used for the preparation of the three key fragments, was prepared in nine steps and 59% overall yield from p-methoxybenzyl alcohol. The α,β-unsaturated ester was converted into alkyne 10 in six additional steps and Weinreb amide 11 in three steps. Weinreb amide 11 was then treated with the lithiated alkyne to arrive at ynoate 9 in 87% yield (Scheme 1.2). Deprotection of the triethylsilyl (TES) protecting groups with pyridinium p-toluenesulfonate (PPTS) in methanol triggered spontaneous formation of mixed acetal 13 in 97% yield. As a consequence of utilizing α,β-unsaturated ester 12 as a common intermediate, inversion of the C11 stereocenter was required. Toward this end, mixed acetal 13 was converted to the mesylate, which upon cleavage of the p-methoxybenzyl ether and treatment with base effected formation of the epoxide with concurrent inversion of the C11 stereocenter. Subjection of the alkyne to hydrogenation conditions and treatment with PPTS in methanol delivered mixed acetal 14 as a single stereoisomer. Epoxide 14 was then treated with lithiated propyne to install the alcohol at C11 with the correct stereochemistry. Following exposure of the mixed acetal to PPTS in methanol for a third time, a thermodynamic

Scheme 1.1. Shimizu's retrosynthetic analysis.
mixture of spiroketals 15 and 16 (10:7 15S/15R) was obtained as an inseparable mixture. Regioselective formation of the vinyl iodide and silyl deprotection rendered the spiroketals separable, allowing for isolation of 7 and 8 in 45% and 30% yield, respectively. Extensive 2-D NMR analysis of spiroketals 7 (15S) and 8 (15R) was employed to assign the major product (7) as the spiroketal corresponding to the spirofungin A core.

**Scheme 1.2. Synthesis of spiroketals 7 and 8.**

Spiroketals 7 and 8 were independently carried through the remaining steps in the synthesis (Scheme 1.3). First, the C20-C24 diene was installed via a Horner-Wadsworth-Emmons olefination of the aldehydes prepared from 7 and 8 with phosphonate 6 in 96% and 86% yield, respectively. The Suzuki coupling of vinyl iodide 17 or 18 with vinyl boronate 5, derived from common intermediate 12 in five steps, efficiently installed the C1-C6 side chain and completed the carbon framework of the natural product. Finally, hydrolysis of the diesters with lithium hydroxide and
deprotection of the tert-butylidemethylsilyl (TBS) ether provided (+)-spirofungin A (1) in 74% yield or (-)-spirofungin B (2) in 80% yield over the final three steps. This first total synthesis of spirofungins A and B by Shimizu provided the natural products in 31 steps over the longest linear sequence, with overall yields of 7.9% and 5.2% for spirofungin A and B, respectively.

**Scheme 1.3.** Total synthesis of spirofungins A and B.

\[
\begin{align*}
\text{Scheme 1.3. Total synthesis of spirofungins A and B.} \\
\begin{array}{c}
\text{1. Dess-Martin periodinane} \\
\text{2. LiHMDS, THF-HMPA} \\
\text{17: 96% (2 steps)} \\
\text{18: 86% (2 steps)} \\
\text{1. Pd(PPh\textsubscript{3})\textsubscript{4}} \\
\text{TIOEt, THF} \\
\text{2. LiOH} \\
\text{THF/MeOH/H\textsubscript{2}O} \\
\text{3. n-Bu\textsubscript{4}NF, DMAP} \\
\text{(-)-1: 74% (3 steps)} \\
\text{(+)-2: 80% (3 steps)} \\
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 1.3. Total synthesis of spirofungins A and B.} \\
\begin{array}{c}
\text{1. Dess-Martin periodinane} \\
\text{2. LiHMDS, THF-HMPA} \\
\text{17: 96% (2 steps)} \\
\text{18: 86% (2 steps)} \\
\text{1. Pd(PPh\textsubscript{3})\textsubscript{4}} \\
\text{TIOEt, THF} \\
\text{2. LiOH} \\
\text{THF/MeOH/H\textsubscript{2}O} \\
\text{3. n-Bu\textsubscript{4}NF, DMAP} \\
\text{(-)-1: 74% (3 steps)} \\
\text{(+)-2: 80% (3 steps)} \\
\end{array}
\end{align*}
\]

**ii. Kozmin’s synthesis of spirofungin A**

The Kozmin group devised an elegant approach towards the stereoselective synthesis of spirofungin A.\(^6\) Similar to Shimizu’s approach, Kozmin and co-workers sought to prepare spiroketal core 20 and then install the unsaturated side chains at a late stage via a Horner-Wadsworth-Emmons reaction and a palladium catalyzed coupling reaction with vinyl stannane 19 (Scheme 1.4). It was envisioned that spiroketal 21 could be formed selectively from ketone 22, wherein a temporary silyl tether would influence the spatial orientation of the side chains, allowing for exclusive formation of the spirofungin A spiroketal.\(^{31,32}\) Ketone 22 would be prepared from terminal olefins 23 and 24 via the cyclopropenone acetal ring opening/cross metathesis methodology developed by Kozmin.\(^{33}\)
The synthesis commenced with the ring opening/cross metathesis sequence between olefin 23 and cyclopropenone acetal 25. Upon subsequent cleavage of the TBS ether, 26 was obtained in 60% yield over 2 steps (Scheme 1.5). Introduction of the dialkoxy silane tether was achieved upon sequential addition of alcohols 26 and 24 to a mixture of dichlorodi-iso-propylsilane. Subsequent cleavage of the acetal and ring closing metathesis with Grubbs 2\textsuperscript{nd} generation catalyst (G2)\textsuperscript{34} afforded ketone 22 in 55% yield over the three step sequence. Exposure of dienone 22 to hydrogenation conditions resulted in reduction of the dienone with concomitant debenzylatation and spiroketalization to give rise to spiroketal 21 exclusively in 98% yield.
Removal of the temporary silyl tether with tetrabutylammonium fluoride, followed by oxidative cleavage of the resultant 1,2-diol, formation of the C20 TBS ether, and Wittig olefination provided vinyl dibromide 20 (Scheme 1.6). Installation of the right hand side chain was achieved by successive palladium catalyzed coupling reactions with vinyl dibromide 20. An E-selective Stille coupling$^{35}$ with vinyl stannane 19 was followed by a Negishi coupling$^{36}$ with dimethylzinc to generate terminal olefin 27 in 60% yield. A cross metathesis reaction with methyl acrylate$^{37}$ completed the C1-C8 side chain; subsequent removal of the C20 TBS ether afforded alcohol 28 in 52% yield over the two steps. To complete the synthesis, appendage of the C20-C24 side chain was accomplished by a four step sequence. After removal of the C20 TBS ether, a similar sequence to that described by Shimizu$^{5}$ was employed to give rise to spirofungin A (1) in 20 steps over the longest linear sequence and 2.9% overall yield.
iii. **Rizzacasa’s synthesis of spirofungin A**

The most recent synthesis of spirofungin A was disclosed by Rizzacasa shortly after our synthesis of spirofungins A and B.\(^{15}\) Rizzacasa and co-workers have shown considerable interest in this family of natural products, having reported the total synthesis of reveromycin A\(^{38,39}\) and B,\(^{40,41}\) the initially proposed structure of spirofungin B,\(^4\) and the total synthesis of spirofungin A.\(^{15}\) Their synthesis features a more traditional acid-catalyzed spiroketalization strategy, followed by a hydrogen bond controlled epimerization to prepare spirofungin A exclusively. Retrosynthetically, as in the previous two syntheses, they planned to append the side chains to an orthogonally substituted spiroketal core. Spiroketal 29 would be prepared from ketone 30, which in turn could be accessed from Weinreb amide 31 and terminal olefin 32 (Scheme 1.7).
Spiroketal precursor 30 was prepared from Weinreb amide 31 and alkene 32 in three steps via a vinyl addition, cross metathesis, hydrogenation sequence in excellent overall yield (Scheme 1.8). Initial treatment of ketone 30 with PPTS in methanol resulted in a 1:2 mixture of spiroketals 34 (15S) and 35 (15R), in which the spirofungin B core (15R) was favored.

At this point in their synthesis, considerable effort was directed toward epimerization of the spiroacetal center to prepare spirofungin A in a more selective manner. Simply resubjecting undesired spiroketal 35 (15R) to the identical conditions resulted in epimerization to the previously obtained 1:2 mixture. As this was not an efficient way to funnel material towards spirofungin A, the mixture of spiroketals was
carried forward with the intention of exploring epimerization at a later stage in the synthesis. Spiroketalts 34 and 35 were converted to alkynes 36 and 37 in three steps via hydrogenolysis of the benzyl ether, Dess-Martin oxidation, and an Ohira-Bestmann reaction (Scheme 1.9). To remove the TBS ether, the mixture of spiroketalts 36 and 37 was treated with a catalytic amount of CSA in methanol and methylene chloride. To their delight, these conditions not only effected the TBS deprotection, but also increased the ratio of spiroketal 29 (15S) to 38 (15R) to 9:1. The spiroketalts were readily separated at this point, and after one recycle of the undesired spirofungin B core, spiroketal 29 was obtained in a >99:1 ratio.

In an attempt to streamline the synthesis, ketone 30 was treated directly with CSA in methanol, from which a disappointing 1:1.4 ratio of spiroketalts 39 to 40 was obtained in 91% yield (Scheme 1.10). This result provided convincing evidence that the free alcohol alone had little influence on the stereochemical outcome of the spiroketalization. The unique combination of the free alcohol and the axial alkyne allows for the thermodynamically favored spiroketal 29 (15S) to be formed with exceptional selectivity. The dramatic increase in thermodynamic preference for the spirofungin A core is explained by the decrease in size of the C20 substituent (alkyne vs. benzyl.
ether), as well as an intramolecular hydrogen bonding interaction (See Scheme 1.9). As both spiroketals 29 and 38 were crystalline, X-ray analysis confirmed the interaction between the primary alcohol and the endocyclic oxygen in 29, but there was no evidence of intramolecular hydrogen bonding in the minor diastereomer, 38.

**Scheme 1.10.** Exploration of spiroketal selectivity with ketone 30.

With spirofungin A core 29 in hand, installation of the right hand side chain was the next task at hand (Scheme 1.11). A more stepwise approach than in the previous syntheses was employed, in which Dess-Martin oxidation of 29 followed by successive Wittig reactions appended the C6-C8 diene functionality. A reduction-oxidation sequence afforded aldehyde 42, which was employed in a tin triflate mediated syn aldol reaction with oxazolidinethione 43,44 delivering aldol adduct 44 in 75% yield from 41. Reductive removal of the chiral auxiliary and protection of the resultant secondary alcohol as the TBS ether afforded 45 in 40% yield over the three step sequence.

**Scheme 1.11.** Elaboration of the spiroketal core.
Attention was then turned to introduction of the C20-C24 side chain. Hydrostannylation of alkyne 45, followed by a Stille coupling of vinyl iodide 47 with the resultant vinyl stannane 46 generated ester 48 in 82% yield (Scheme 1.12). To complete the total synthesis, Rizzacasa employed a similar four step sequence to that utilized by both Shimizu and Kozmin, to arrive at spirofungin A (1) in 23 steps and 3.0% overall yield from the previously prepared Weinreb amide 31; 30 steps from commercially available starting materials.  

**Scheme 1.12.** Total synthesis of spirofungin A.
2.1 Retrosynthetic analysis

As in the previously reported syntheses of spirofungins A and B, we sought to divide the molecule into three key fragments: C1-C6 right hand side chain 49, C21-C24 left-hand side chain 50, and spiroketal core 51 or 52 (Scheme 2.1). It was envisioned that the spirofungins could be constructed in an efficient manner by employing a late stage cross metathesis reaction to append the unsaturated acid side chains to the spiroketal core. Spiroketal core 51 or 52 would arise from the acid-catalyzed spiroketalization of ketone 53, available from β-ketophosphonate 54 and aldehyde 55 via a Horner-Wadsworth-Emmons, conjugate reduction sequence. β-Ketophosphonate 54 and C1-C6 side chain 49 would be prepared from a common intermediate using the thiazolidinethione-mediated propionate aldol reaction developed in our laboratories. 47 Aldehyde 55 would be derived from a chiral auxiliary mediated acetate aldol reaction. 48
2.2 Synthesis of the spiroketal core

i. Synthesis of aldehyde 55

Efforts toward the spiroketal core began with the synthesis of aldehyde 55. Due to the requisite anti substitution of aldehyde 55, this fragment could not be accessed directly via a thiazolidinethione-mediated propionate aldol reaction. Instead, aldehyde 55 was prepared via a diastereoselective acetate aldol reaction followed by a Frater-Seebach alkylation.\textsuperscript{49,50} The acetate aldol reaction between mesityl substituted N-acetylthiazolidinethione 56 and 3-butenal\textsuperscript{51} gave rise to aldol adduct 57 in 80% yield and excellent diastereoselectivity (>20:1) (Scheme 2.2).\textsuperscript{48} Direct displacement of the chiral auxiliary with methanol or iso-butyl alcohol provided ester 58 or 59 in 100% and 98% yield, respectively.\textsuperscript{47}

Scheme 2.1. Retrosynthetic analysis of spirofungins A and B.
which TMEDA was employed as an additive, provided alkylated product 60 with high diastereoselectivity, albeit in modest yield (entry 1).\textsuperscript{52} With iso-butyl ester 59, promising results were obtained when the Frater-Seebach alkylation was run in the absence of an additive while raising the temperature to $-40^\circ C$ (entry 2). After screening a variety of other conditions, it was determined that employing DMPU as an additive resulted in the highest yields for both the methyl and iso-butyl esters (Table 2.1, entries 3-4).\textsuperscript{53}

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Additive</th>
<th>Temperature</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>TMEDA</td>
<td>$-78^\circ C$</td>
<td>36%</td>
</tr>
<tr>
<td>2</td>
<td>i-Bu</td>
<td>none</td>
<td>$-78^\circ C$ to $-40^\circ C$</td>
<td>47%</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>DMPU</td>
<td>$-78^\circ C$ to $0^\circ C$</td>
<td>37-61%</td>
</tr>
<tr>
<td>4</td>
<td>i-Bu</td>
<td>DMPU</td>
<td>$-78^\circ C$ to $0^\circ C$</td>
<td>55-68%</td>
</tr>
</tbody>
</table>

At best, these conditions provided methyl ester 60 in 61% yield or iso-butyl ester 61 in 68% yield. As a result of the slightly higher yield obtained for the Frater-Seebach alkylation with iso-butyl ester 59, we proceeded with alkylated ester 61 towards aldehyde 55. Protection of the secondary alcohol as the triethylsilyl (TES) ether, followed by treatment with di-iso-butylaluminum hydride gave rise to aldehyde 55 in 89% yield over the two step sequence (Scheme 2.3). With the optimized conditions, aldehyde 55 could be generated in five steps and 46% overall yield.

\textbf{Scheme 2.3.} Synthesis of aldehyde 55.
ii. **Synthesis of the \( \beta \)-ketophosphonate**

Attention was then turned to the synthesis of the \( \beta \)-ketophosphonate via a thiazolidinethione mediated propionate aldol reaction. The synthesis commenced with an Evans-syn propionate aldol reaction between \( N \)-propionylthiazolidinethione 63 and acrolein to deliver aldol adduct 64 in 96% yield and >20:1 diastereomeric ratio (Scheme 2.4).\(^{47}\) The resultant secondary alcohol was protected as the TES ether and reductive removal of the chiral auxiliary with di-iso-butylaluminum hydride furnished aldehyde 65 in 94% yield over the two steps.

**Scheme 2.4. Synthesis of aldehyde 65.**

In the literature, we encountered the seldom used ylide-phosphonate 67,\(^{54}\) which seemed perfectly suited for use in our synthesis. This reagent would allow us to access \( \beta \)-ketophosphonate 68 in just four steps from acrolein. Ylide-phosphonate 67 was prepared from 1,3-dibromoacetone in 3 steps (Scheme 2.5). The displacement of one of the bromides with triphenylphosphine, followed by ylide formation delivered ylide 66 in 81% yield.\(^{55,56}\) The phosphonate was installed upon treatment of ylide 66 with diethyl phosphite and sodium hydride, generating ylide-phosphonate 67 in 68% yield.

**Scheme 2.5. Synthesis of ylide-phosphonate 67.**

Limited procedural details were provided in the original publication for use of this reagent in olefination reactions;\(^{54}\) thus, it was necessary to investigate conditions for promoting the desired bond-forming event between aldehyde 65 and ylide-phosphonate...
With the intent of performing the Wittig reaction prior to the Horner-Wadsworth-Emmons olefination to arrive at β-ketophosphonate 68, we initially ran the reaction in refluxing THF for 24 hours, only to recover aldehyde 65 unreacted (entry 1). We next turned to higher boiling solvents, such as toluene and chlorobenzene, both of which resulted in minimal product formation even at extended reaction times (entries 2-3). Concerned that the prolonged reaction times at elevated temperatures were leading to ylide decomposition, several reactions were conducted at temperatures ranging from 50 to 70 °C over several days (entries 4-6). Despite variation in the reaction time, temperature, solvent, and equivalents of aldehyde 65 and ylide-phosphonate 67, at best, a 38% yield of β-ketophosphonate 68 was obtained.

### Table 2.2. Optimization of the Wittig reaction with ylide-phosphonate 67.

<table>
<thead>
<tr>
<th>Entry</th>
<th>65 (equiv)</th>
<th>67 (equiv)</th>
<th>solvent</th>
<th>temp, time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>1.5</td>
<td>THF</td>
<td>70 °C, 24 h</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>3.0</td>
<td>Toluene</td>
<td>110 °C, 2 d</td>
<td>38%</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>2.0</td>
<td>Chlorobenzene</td>
<td>130 °C, 24 h</td>
<td>26%</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>1.0</td>
<td>Toluene</td>
<td>50 °C, 6 d</td>
<td>17%</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>1.0</td>
<td>Toluene</td>
<td>rt, 6 d</td>
<td>21%</td>
</tr>
<tr>
<td>6</td>
<td>1.0</td>
<td>3.0</td>
<td>THF</td>
<td>70 °C, 5 d</td>
<td>33%</td>
</tr>
</tbody>
</table>

As this was not an efficient way to advance material, we next turned our attention to stabilized ylide 69 to homologate the aldehyde to α,β-unsaturated ester 70 (Scheme 2.6). While employing this ylide increased the number of steps necessary to prepare the β-ketophosphonate, the vast improvement in yield made this route more advantageous. Ester 70 also serves as a common intermediate in the synthesis of the β-ketophosphonate and C1-C6 side chain 49. Finally, the treatment of ester 70 with
lithiated dimethylmethyl phosphonate\textsuperscript{57} generated $\beta$-ketophosphonate 71 in five steps and 65\% overall yield.

\textbf{Scheme 2.6. Synthesis of $\beta$-ketophosphonate 71.}

With both $\beta$-ketophosphonate 71 and aldehyde 55 in hand, formation of the spiroketal precursor via a modified Horner-Wadsworth-Emmons olefination was explored (Scheme 2.7). Treatment of $\beta$-ketophosphonate 71 with barium hydroxide followed by addition of aldehyde 55 formed the desired C13-14 bond in 73\% yield.\textsuperscript{58} Conjugate reduction of dienone 72 was attempted with nickel chloride and sodium borohydride in the presence of methanol.\textsuperscript{59,60} We opted for these conditions anticipating that the presence of methanol in the reaction would enable the selective reduction of both of the $\alpha,\beta$-unsaturated systems in dienone 72. Unfortunately, a 9:1 ratio of enones 73 and 74 in 55\% yield were the only products obtained. The spiroketal precursor, ketone 53, could be accessed upon resubjection of the mixture of enones to the same conditions, albeit in only 38\% yield from dienone 72.

\textbf{Scheme 2.7. Synthesis of ketone 53.}
These results prompted us to take a more stepwise approach toward ketone 53, in which conjugate reduction of 70 would be carried out prior to formation of the β-ketophosphonate. Toward this end, 1,4-reduction of ester 70 with di-iso-butylaluminum hydride mediated by MeCu, delivered saturated ester 75 in 93% yield (Scheme 2.8). Subsequent treatment of ester 75 with lithiated dimethyl methylphosphonate furnished β-ketophosphonate 76 in 93% yield and 73% overall yield for the six steps.

It is noteworthy that while this sequence for preparing β-ketophosphonate 76 requires six steps, the 73% overall yield is significantly higher than both the four step sequence with ylide-phosphonate 67 and the five step sequence in which the β-ketophosphonate was formed directly from α,β-unsaturated ester 70.

**iii. Construction of the spiroketal core**

From β-ketophosphonate 76 and aldehyde 55, ketone 53 was prepared in 77% yield over two additional steps by a Horner-Wadsworth-Emmons olefination, conjugate reduction sequence (Scheme 2.9). To arrive at the spiroketal core, ketone 53 was treated with PPTS in methanol to induce cleavage of the triethyldisilyl (TES) protecting groups and spontaneous spiroketalization, to give rise to a 1:2 mixture of spiroketal 78 and 79 in a combined 90% yield.
Correlation of the characteristic signals for the protons at C11 and C19 of the $^1$H NMR spectrum to similar intermediates from Shimizu's synthesis, in addition to 2-D NOESY and COSY NMR analysis, confirmed that the major product corresponded to the spiroketal core of spirofungin B. The 2-D NOESY NMR data of minor spiroketal 78 showed a strong cross peak between the protons at C11 and C20, while spiroketal 79 showed a cross peak between the protons at C11 and C19, supporting the assignment of the major product as the spirofungin B core (Figure 2.1).

Various acidic conditions were investigated in an effort to increase the selectivity for spirofungin A core 78, but all efforts resulted in a similar 1:2 ratio. Epimerization of the C15 spirocenter of the spirofungin B core was also explored; however, when spiroketal 79 was exposed to PPTS in methanol or CSA in methylene chloride, no change was observed and spiroketal 79 was recovered cleanly. While it was expected that the spirofungin A core would be favored, it was known that these spiroketals would
be very similar in energy. Upon comparison of spiroketsals 78 and 79 to the spiroketsals from Shimizu\(^5\) and Rizzacasa’s synthesis,\(^15\) it is evident that subtle changes at the terminus of the spiroketal precursor can have a dramatic effect on the stereochemical outcome of the spiroketalization.

Despite the poor selectivity for the spirofungin A core, we moved forward with the synthesis with the intention of epimerizing the spirocenter at a later stage. Upon separation via flash column chromatography, spiroketsals 78 (15S) and 79 (15R) were obtained in 30% and 60% yield, respectively, and carried on separately for introduction of the unsaturated side chains. We opted to install the diene via a sequential cross metathesis/methylene Wittig olefination (Scheme 2.10).\(^62\) The treatment of 78 or 79 with methacrolein and 5 mol % Grubbs 2\(^{nd}\) generation catalyst (G2) gave rise to an intermediate enal, which upon methylene Wittig olefination\(^63\) introduced the terminal olefin, providing dienes 51 and 52 in 49% and 65% yield, respectively.

**Scheme 2.10.** Synthesis of spiroketsals 51 and 52.

2.3 Installation of the C1-C6 side chain

i. *Literature precedent for the key cross metathesis reaction*

Having developed an efficient route to the spiroketal core, focus was shifted to the synthesis and appendage of the unsaturated side chains to spiroketal 51 or 52 via cross metathesis. Attention was first turned to installation of C1-C6 side chain 49. Over the years, cross metathesis has been widely used in total synthesis; however, few
examples exist in which a similarly substituted diene, a Type III olefin, and an allylic alcohol, a Type II olefin, undergo a cross metathesis reaction. One example of a comparable cross metathesis comes from the synthesis of apoptolidinone completed by our group. The synthesis features a highly selective cross metathesis between diene 82 and trienoate 83 to arrive at advanced intermediate 84 in 63% yield (Scheme 2.11).

**Scheme 2.11.** Literature precedent for key cross metathesis reaction.

Based on this strong literature precedent, we proceeded with a model system to optimize conditions for our proposed cross metathesis. Previously prepared ester 62 was identified as a suitable model system, as upon installation of the C6-C8 diene, this fragment maps onto the right-hand portion of the spiroketal core (Scheme 2.12). The same cross metathesis/methylene Wittig sequence was employed to arrive at model diene system 86 in 50% yield.

**Scheme 2.12.** Synthesis of the model C6-C8 diene.

The desired C1-C6 side chain could be generated in one step from unsaturated ester 70, an intermediate from the synthesis of β-ketophosphonate 76, in 92% yield.
Thus, C1-C6 side chain 49 was prepared in five steps and 76% overall yield.

**Scheme 2.13.** Synthesis of C1-C6 side chain 49.

With both C1-C6 side chain 49 and model diene 86 in hand, optimization of the key cross metathesis reaction was carried out. Our first task was identification of the optimal metathesis catalyst. Exposure of diene 86 and C1-C6 side chain 49 to Grubbs 2nd generation catalyst (G2) or Hoveyda-Grubbs 2nd generation catalyst (HG2) in methylene chloride at room temperature resulted in a modest 28% and 17% yield of cross metathesis adduct 87, respectively (Table 2.3, entries 1-2). Encouragingly, a majority of diene 86 was recovered unreacted, an indication that the poor yields could be attributed to low conversion, not decomposition of the starting material. Since a higher yield was obtained with G2, we decided to focus on this catalyst for the remainder of our optimization studies. In an effort to improve the rate of conversion, we opted to add the ruthenium catalyst to the reaction via syringe pump over several hours. This strategy would allow us to introduce active catalyst over the course of the reaction, thereby circumventing low conversion as a result of catalyst decomposition. Without changing any other experimental parameters, this simple procedural modification increased the yield to 48% (entry 3). A 62% yield of cross metathesis adduct 87 was obtained when the reaction was run at an elevated temperature, comparable to the yield from the similar cross metathesis in the apoptolidinone synthesis (entry 4).
### Table 2.3. Model studies on the key cross metathesis reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Rate of catalyst addition</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>G2</td>
<td>1 portion</td>
<td>23 °C, 24 h</td>
<td>28% (68% brsm)</td>
</tr>
<tr>
<td>2</td>
<td>HG2</td>
<td>1 portion</td>
<td>23 °C, 24 h</td>
<td>17% (98% brsm)</td>
</tr>
<tr>
<td>3</td>
<td>G2</td>
<td>syringe pump addition (8 h)</td>
<td>23 °C, 24 h</td>
<td>48%</td>
</tr>
<tr>
<td>4</td>
<td>G2</td>
<td>syringe pump addition (8 h)</td>
<td>40 °C, 24 h</td>
<td>62%</td>
</tr>
</tbody>
</table>

### iii. Cross metathesis to install the C1-C6 side chain

Pleased with the yield obtained with the model system, our focus returned to the cross metathesis between spiroketals 51 or 52 and C1-C6 side chain 49. Unlike the model system, in which the diene was the only olefin functionality present, the spiroketals necessary for the synthesis possess two terminal olefins. It was expected that the diene would be more reactive towards cross metathesis with C1-C6 side chain 49 than the allylic alcohol embedded in the tetrahydropyran at C19; unfortunately, this proved not to be the case (Scheme 2.14). When a mixture of C1-C6 side chain 49 and spiroketal core 51 was treated with 20 mol % Grubbs 2nd generation catalyst (G2) in methylene chloride, a disappointing 20% yield of the desired cross metathesis product was obtained. More discouraging was the discovery that this material was actually a 1:1 of mixture of desired cross metathesis product 88 and undesired cross metathesis adduct 89, formed as a result of a non-selective cross metathesis reaction.
The lack of discrimination between the terminal olefins at C7 and C20 in spiroketal 51 led us to consider an alternative substrate for the installation of the C1-C6 side chain, in which there would be a stronger bias for reaction with the terminal olefin at C7. We envisaged that ketone 90, derived from the spiroketal precursor, would fulfill this role as the triethylsilyl protecting group of the allylic alcohol at C19 would hinder the cross metathesis reaction from occurring at this site (Scheme 2.15). Upon installation of the C6-C8 diene to ketone 53 via the sequential cross metathesis/Wittig reaction, diene 90 was obtained in 57% yield. Unlike the previous cross metathesis substrate, in which the spiroketal was formed prior to installation of the C6-C8 diene, ketone 53 required addition of precisely one equivalent of methylene triphenylphosphorane to avoid olefination of the C15 ketone. Using the previously optimized conditions in which Grubbs 2nd generation catalyst (G2) was added dropwise to diene 90 and allylic alcohol 49, the desired cross metathesis product was obtained exclusively in 70% yield, with no evidence of the product from the reaction of C1-C6 side chain 49 with the terminal olefin at C20.
2.4. Installation of the C21-C24 unsaturated side chain

i. Attempts to append the C21-C24 fragment via cross metathesis

From ketone 91, three steps remained in the total synthesis of the spirofungins, including introduction of the C21-C24 fragment. The C21-C24 side chain was available in three steps from pyruvic aldehyde dimethyl acetal (Scheme 2.16). A Horner-Wadsworth-Emmons olefination, followed by acetal hydrolysis unveiled an intermediate aldehyde, which upon a methylene Wittig reaction furnished diene 50 in 55% overall yield.\(^{67-69}\)

Scheme 2.15. Cross metathesis to append C1-C6 side chain 49.

![Scheme 2.15](image)

Scheme 2.16. Synthesis of diene 50.

![Scheme 2.16](image)

Our initial attempt to append the C21-C24 diene involved a cross metathesis reaction between diene 50 and ketone 91. Not surprisingly, as the triethylsilyl ether at C19 had been utilized in the previous cross metathesis to inhibit reaction from occurring at this site, no reaction between diene 50 and ketone 91 occurred in the presence of either Grubbs 2\(^{\text{nd}}\) generation catalyst (G2) or the more reactive Hoveyda-Grubbs 2\(^{\text{nd}}\) generation catalyst (HG2) (Scheme 2.17).
As the olefin at C20 had exhibited reactivity towards allylic alcohol 49 when embedded in the spiroketal core, we next turned our attention to the spiroketal derived from ketone 91 as a suitable cross metathesis substrate. Exposure of ketone 91 to PPTS in methanol resulted in a 90% yield of a 1:2 mix of spiroketal 94 and 95, in which the spirofungin B core was favored (Scheme 2.18). The mixture of spiroketal 94 and 95 and diene 50 was then treated with either G2 or HG2; disappointingly, no product formation was observed. Variation of the temperature and catalyst loading was also explored; however, these efforts were unproductive as none of the desired product was obtained.

In order to determine if diene 50 was a competent cross metathesis partner, we attempted the cross metathesis with C1-C6 side chain 49, which maps onto the left-hand
portion of the spiroketal core (Scheme 2.19). To our delight, the cross metathesis between diene 50 and allylic alcohol 49 proceeded smoothly in the presence of 5 mol % Grubbs 2nd generation catalyst to generate dienoate 98 in 83% yield.

**Scheme 2.19.** Model cross metathesis with diene 50.

![Diagram of Scheme 2.19](image)

It was thought that this model could be applied to our synthesis if we could arrive at a derivative of ketone 91 bearing a free alcohol at C20. Straightforward removal of the triethylsilyl protecting groups was not a feasible option as spontaneous spiroketalization would occur. Consequently, the ketone needed to be converted to a masked form prior to deprotection of the triethylsilyl groups. The first option we chose to explore was masking the ketone as a thioketal (Scheme 2.20). Unfortunately, attempts to install the thioketal from ketone 90 with ethanethiol and zinc triflate resulted in a 1:2 ratio of spiroketals 51 and 52, providing evidence that the triethylsilyl groups were too acid labile to withstand the Lewis acidic conditions required to effect thioketal formation.

**Scheme 2.20.** Formation of the thioketal from ketone 90.

![Diagram of Scheme 2.20](image)

As a result, ketone 99, bearing the more robust tri-iso-propylsilyl (TIPS) protecting groups, was prepared using a sequence analogous to that developed for the synthesis of ketone 53. With bis-TIPS ketone 99 in hand, formation of the thioketal could be realized using the previous conditions to afford thioketal 100 in 75% yield (Scheme 2.21). Disappointingly, when thioketal 132 was utilized in the key cross metathesis reaction, cross metathesis adduct 100 was obtained in an unacceptable 16%
yield. We speculate that the low yield may be a result of the presence of the thioketal, as sulfur is capable of coordinating to the catalyst, rendering it inactive.

**Scheme 2.21.** Cross metathesis with thioketal 100.

We next considered an acetal strategy for masking the ketone. With the acid stable TIPS protecting groups in place, we were optimistic that ketone 102 could withstand the conditions necessary for acetal formation (Scheme 2.22). This indeed proved to be the case, as acetal 103 was prepared in 68\% yield upon treatment of ketone 102 and 2,2-dimethyl-1,3-propanediol with PPTS in the presence of molecular sieves. Introduction of the C6-C8 diene was achieved by the previously used cross metathesis/Wittig sequence to give rise to diene 104 in 70\% yield. The cross metathesis with the C1-C6 side chain was then carried out to give rise to cross metathesis adduct 105 in a modest 35\% yield.
Prior to investing the time to address the low yield obtained for the key cross metathesis between acetal 104 and C1-C6 side chain 49, we wanted to ensure that the subsequent reactions could be carried out as planned. We intended to remove the silyl protecting groups from acetal 105 to reveal the free alcohol at C20, perform the cross metathesis with C21-C24 diene 50, and subsequently reveal the ketone to effect spiroketalization. Toward this end, deprotection of the TIPS protecting groups was explored (Scheme 2.23). Due to the acid sensitivity of the acetal, we were limited to using fluoride sources to cleave the TIPS ethers. With tetrabutylammonium fluoride (TBAF) and tris(dimethylamino) sulfonium difluorotrimethylsilicate (TASF), an anhydrous fluoride source, none of the desired triol 106 was obtained.
ii. Incorporation of the C21-C24 side chain via aldol reaction

As a result of these unsuccessful attempts to install C21-C24 side chain 50 via cross metathesis, we decided to incorporate this fragment at an earlier stage in the synthesis. We deemed the most straightforward manner for installing the C21-C24 side chain would be during the aldol reaction, in which we would employ known aldehyde 109 instead of acrolein.\textsuperscript{70-72} Appending this fragment at the beginning of the synthesis would minimize deviation from the original synthetic plan.

Aldehyde 109 was prepared in three steps from 107, available from an allylic oxidation of the tert-butyldimethylsilyl ether of 3-methyl-2-buten-1-ol (Scheme 2.24).\textsuperscript{73} The treatment of aldehyde 107 with ylide 69 gave rise to dienoate 108 in 83% yield. Reduction of the ester with di-iso-butylaluminum hydride and subsequent manganese dioxide oxidation delivered aldehyde 109 in quantitative yield.

\textbf{Scheme 2.23.} Deprotection of acetal 105 to reveal triol 106.

Gratifyingly, aldehyde 109 performed well in the Evans syn aldol reaction with thiazolidinethione 63 to give rise to aldol adduct 110 in 88% yield and >20:1 diastereomeric ratio (Scheme 2.25). As before, the resultant secondary alcohol was protected as the triethylsilyl ether, and the chiral auxiliary reductively cleaved to deliver aldehyde 111 in 81% yield over the two steps. The aldehyde was converted to β-ketophosphonate 112 via the three step sequence utilized for the preparation of β-ketophosphonate 76. Thus, the revised β-ketophosphonate, to which the C21-C24 chain has already been incorporated, was obtained in six steps and 48% overall yield from known aldehyde 109.

Scheme 2.25. Synthesis of β-ketophosphonate 112.

2.5 Completion of the total synthesis of spirofungins A and B

With revised β-ketophosphonate 112 and aldehyde 55 in hand, formation of the spiroketal precursor via a modified Horner-Wadsworth-Emmons olefination was explored. Treatment of 112 with barium hydroxide followed by addition of aldehyde 55 formed the desired C13-14 bond (Scheme 2.26). Conjugate reduction of the resultant enone generated ketone 113 in 94% yield.61
Initially, we sought to append C1-C6 side chain 49 to the rest of the molecule by a cross metathesis reaction with the diene derived from ketone 113, as this sequence had provided the best results with the previous substrates. Additionally, this route would offer the advantage of postponing the spiroketalization until the final steps, minimizing the number of transformations which would have to be carried out on the independent spiroketals. Introduction of the C6-C8 diene to ketone 113 was achieved via the two step cross metathesis/methylene Wittig sequence (Scheme 2.27). With this particular substrate, the methylene Wittig reaction proved quite problematic. After initially obtaining diene 115 in 60% yield, these same results could not be obtained consistently, with yields ranging from 8-40%. As a consequence of requiring precisely one equivalent of methylene triphenylphosphorane, the reaction was plagued by low rates of conversion, despite taking extensive measures to exclude moisture from the reaction. When a slight excess of methylene triphenylphosphorane was employed in the reaction, bis-olefinated product 116 was obtained; in addition, unreacted aldehyde 114 was also recovered from the reaction mixture. Crystallized, salt-free methylene triphenylphosphorane, which can be added as a solution throughout the course of the reaction, was also explored.\textsuperscript{74} Significant variation in the yield for the methylene Wittig was also observed with the salt-free ylide, with yields ranging from 20-69%.

![Scheme 2.26. Synthesis of ketone 113.](image-url)
Although we were not satisfied with these results, we decided to push forward and investigate the cross metathesis reaction, with the intention of optimizing the Wittig after assessing the viability of the remaining steps in the synthesis. Toward this end, the cross metathesis reaction between ketone 115 and C1-C6 side chain 49 was carried out using the previously optimized conditions to afford cross metathesis adduct 117 in 50% yield (Scheme 2.28). Ketone 117 contains the entire carbon skeleton of the natural product with spiroketalization, adjustment of the oxidation state at C24, and hydrolysis the ethyl ester as the only remaining steps.

**Scheme 2.27.** Methylen Wittig olefination to install the C6-C8 diene.

![Scheme 2.27 Diagram](image)

**Scheme 2.28.** Synthesis of the carbon skeleton of spirofungins A and B.

![Scheme 2.28 Diagram](image)
Exposure of ketone 117 to PPTS in methanol resulted in facile cleavage of the three silyl protecting groups and spontaneous spiroketalization to generate a 2:1 ratio of spiroketals 118 and 119 in a moderate 50% yield. Upon correlation of the characteristic signals corresponding to protons at C11 and C19 to the $^1$H NMR spectra of spiroketals 51 and 52, it was determined that the major product corresponded to the spirofungin A core. Intrigued by the reversal of selectivity, we wanted to probe whether these results could be attributed to the presence of the C1-C6 side chain or the C21-C24 side chain in the spiroketal precursor. Toward this end, ketone 113, which bears the C21-C24 side chain, but not the C1-C6 side chain, was subjected to the identical spiroketalization conditions (Scheme 2.29). Cleavage of the silyl protecting groups with concomitant formation of a 2:1 mixture of spiroketals 120 and 121 resulted. The spiroketals were readily separated by flash column chromatography to give 120 and 121 in 56% and 26% yields, respectively.

**Scheme 2.29.** Spiroketalization of ketone 113.

NOESY and COSY NMR analysis determined that the major product corresponded to the spiroketal core of spirofungin A (Figure 2.2). A strong correlation between the proton at C11 and those at C20 and C21 was observed, confirming the assignment of 120 as the spirofungin A core. Upon comparison of the various spiroketals prepared during the course of our synthetic efforts, it was evident that the presence of the C21-C24 side chain, not the C1-C6 side chain, in the spiroketal precursor has a greater influence on the stereochemical outcome of the spiroketalization.
The significantly higher yield obtained for the spiroketalization of ketone 113 compared to 117, in combination with the inconsistency of the methylene Wittig reaction, caused us reconsider our endgame strategy. We decided to pursue our original synthetic plan, in which we would construct the spiroketal core prior to installation of C1-C6 side chain 49. With the C20-24 side chain already in place, competition between the two terminal olefins during the cross metathesis was no longer an issue.

Moving forward with the synthesis, spiroketalts 120 and 121 were independently carried through the remaining steps. Introduction of the desired oxidation state of C24 was achieved by a manganese dioxide oxidation employing sodium cyanide and methanol to deliver methyl esters 122 and 123 directly from allylic alcohols 120 and 121, each in 78% yield (Scheme 2.30).75,76 To arrive at the desired cross metathesis partner, installation of the C6-C8 diene was accomplished via the previously utilized two-step sequence. Treatment of 122 or 123 with methacrolein and Grubbs 2nd generation catalyst gave rise to enals 124 and 125 each in 74% yield. A methylene Wittig olefination introduced the terminal olefin, providing dienes 126 and 127 in 86% and 75% yield, respectively.

Figure 2.2. Assignment of the spiroketal 120 (15S) based on 2-D NOESY NMR.
The major bond forming event that remained was introduction of the C6-C7 bond via the key cross metathesis reaction between diene 126 or 127 and C1-C6 side chain 49 (Scheme 2.31). The previously optimized conditions for the cross metathesis, in which Grubbs 2nd generation catalyst (G2) was added as a solution over several hours, delivered the cross metathesis products 128 and 129 in 83% and 71% yield respectively, based on recovered diene. Finally, employing conditions used in Shimizu’s synthesis of the spirofungins,5 hydrolysis of diesters 128 and 129 with lithium hydroxide provided (−)-spirofungin A (1) in 87% yield and (+)-spirofungin B (2) in 88% yield.
2.6. Summary

A highly convergent total synthesis of spirofungins A and B was completed in 14 steps as the longest linear sequence from known aldehyde 109, 19 steps from commercially available 3-methyl-2-buten-1-ol. The three key fragments: aldehyde 55, β-ketophosphonate 112, and C1-C6 side chain 49, were all prepared in six steps or less in 46%, 48%, and 76% overall yield, respectively. A highlight of the synthesis is the use of the thiazolidinethione mediated propionate and acetate aldol reactions developed in our laboratories to install five of the seven stereocenters of the natural product. The synthesis also features a demanding cross metathesis reaction, which proved to be an efficient strategy for appending the C1-C6 side chain to the spiroketal core.
CHAPTER THREE

Background: (+)-Sorangicin A

3.1 Isolation

In 1985 (+)-sorangicin A (130) was isolated by Höfle and Reichenbach from Sorangium cellulosum strain So ce12 (Figure 3.1).\textsuperscript{77,78} The producing strain was originally isolated from a soil sample collected in Xcaret, Mexico in 1978. The gliding bacteria (myxobacteria) Sorangium cellulosum, from which sorangicin A was isolated, has been identified as a rich source of structurally diverse secondary metabolites possessing a broad range of bioactivity.\textsuperscript{79} Sorangicin A has shown promise as a broad spectrum antibiotic, as it is active against both Gram-positive and Gram-negative bacteria.\textsuperscript{78} As a result of its significant biological properties and unique structure, sorangicin A was identified as an attractive target for total synthesis.
3.2 Structural determination

Structural elucidation of sorangicin A was carried out primarily using high-resolution mass spectroscopy in combination with extensive 1-D and 2-D NMR analysis. The molecular formula of C_{47}H_{66}O_{11} and molecular weight of 806 g/mol were determined by negative ion fast atom bombardment (FAB) and high resolution electron impact (EI) mass spectroscopy, and confirmed by elemental analysis.\textsuperscript{77,80}

With the molecular formula as a basis for structural assignment, several \textsuperscript{1}H-\textsuperscript{1}H and \textsuperscript{1}H-\textsuperscript{13}C 2-D NMR experiments were conducted to elucidate the structure of sorangicin A. X-ray crystal analysis later confirmed the connectivity and absolute configuration of the natural product.\textsuperscript{80} While the structure and stereochemical assignments originally reported by Höfle and Reichenbach were correct, contradictory reports of the configuration of the C10 stereocenter resulted in several publications in which the stereochemistry at this position was inverted.\textsuperscript{81-89} The stereogenicity at C10 as S, as had been originally reported, was clarified by Jansen in 2008 (See Figure 3.1).\textsuperscript{90}

Sorangicin A contains 15 stereocenters and features a signature bicyclic ether, a tetra-substituted tetrahydropyran, and a tri-substituted dihydropyran all embedded in a 31-membered macrolactone. Additionally, the macrocyclic skeleton is highly unsaturated.
and contains a sensitive \((Z,Z,E)\)-trienoate, to which the instability of the natural product toward several reagents has been attributed.\(^8\)

### 3.3 Biological activity

Prior to the isolation of any myxobacterial antibiotics from *Sorangium cellulosum*, the important role of these bacteria in cellulose degradation in the soil had long been recognized.\(^9\) Reports of the production of antibacterial substances by myxobacteria date back to 1946; however, it was not until the mid-1970s that the structure of a myxobacterial antibiotic was first described. At this time there was a renewed interest in myxobacterial antibiotics, resulting in the characterization of a significant number of biologically active secondary metabolites over the next decade, amongst them, sorangicin A.\(^7\)

Sorangicin A was identified as the main bioactive component of *Sorangium cellulosum* strain Soce12, exhibiting potent activity against both Gram-positive and Gram-negative bacteria. Sorangicin A is especially active towards Gram-positive bacteria, such as *Staphylococcus aureus*, with minimal inhibitory concentration (MIC) values ranging from 0.01 to 0.1 µg/mL. At higher concentrations (3-30 µg/mL) Gram-negative bacteria, such as *Escherichia coli*, are also inhibited, while yeasts and molds are resistant.\(^7\) Interestingly, sorangicin A is active against several myxobacteria (MIC 0.1-3 µg/mL), however, against the producing strain So ce12, higher concentrations (50 µg/mL) were required for inhibition. The exceptional antibiotic activity displayed by sorangicin A makes it the most potent myxobacterial antibiotic isolated to date.\(^7\)

Sorangicin A was found to be an inhibitor of RNA polymerase (RNAP), the enzyme responsible for transcription of DNA into RNA. This mechanism of action is identical to the ansamycin antibiotic rifampin, a known RNAP inhibitor commonly used for the treatment of tuberculosis.\(^8,9\) In the case of sorangicin A and rifampin, inhibition
of RNA polymerization is the result of a steric clash between the RNAP-bound antibiotic and the path of the elongating RNA transcript, resulting in a build-up of RNA transcripts no longer than 2-3 nucleotides. Studies by Jansen and Darst\textsuperscript{82} revealed that sorangicin A and rifamycin bind in the same RNAP β-subunit pocket, despite the fact that these natural products are structurally dissimilar. Interestingly, an X-ray crystal structure of a bacterial RNAP in complex with sorangicin established that the overall shape of sorangicin compared to rifampin in the binding pocket is very similar. In fact, all 12 residues which interact with rifampin also interact with sorangicin.

Jansen and Darst were also responsible for a cross-resistance study which helped illustrate the differences in the way these antibiotics interact with RNAP. Known rifampin-resistant \textit{E. coli} mutants were employed in the cross-resistance study in an effort to determine if these same mutations also resulted in sorangicin resistance. While several mutations led to strong resistance to both sorangicin A and rifampin, in a number of cases, mutations which led to strong resistance against rifampin, showed little or no change in sorangicin binding affinity. This class of mutants, which saw a different response from sorangicin A compared to rifampin, contained residues which were expected to introduce unfavorable steric interactions or alter the shape of the binding pocket. The results of the cross-resistance study indicate a distinct difference between these RNAP inhibitors is the ability of sorangicin to adapt to fluctuations in the shape of the binding pocket, while rifampin is extremely sensitive to changes in conformation. It is speculated that this is a result of the structural rigidity of rifampin as compared to conformational flexibility of sorangicin A. The ability of sorangicin to accommodate distortion of the binding pocket has implications for the further exploration of sorangicin A as an antibiotic.
3.4 Previous synthetic efforts

As one would expect, the complex architecture and important biological activity of (+)-sorangicin A have drawn the attention of the synthetic community. To date, Smith and co-workers have completed the only total synthesis of sorangicin A,\(^9\) with the groups of Schinzer,\(^8\) Lee,\(^8\) Mohapatra,\(^8\) and Srihari,\(^8\) in addition to our own,\(^8\) having published progress towards key fragments of this natural product.

\(i.\) Smith’s total synthesis of (+)-sorangicin A

Smith and co-workers divided (+)-sorangicin A (130) into three key fragments: C16-C29 tetrahydropyran 131, C1-C15 dihydropyran 132, and C30-C38 bicyclic ether core 133 (Scheme 3.1).\(^9\) They envisioned that these three fragments could be assembled by a Julia-Kocienski olefination to form the C15-C16 and C29-C30 bonds. Incorporation of the sensitive (Z,Z,E)-trienoate linkage would be achieved via a late stage Stille reaction with vinyl stannane 134.

\textbf{Scheme 3.1. Smith’s retrosynthetic analysis.}

In a 2005 communication, the Smith group disclosed their routes towards C16-C29 tetrahydropyran (THP) 131 and C1-C15 dihydropyran (DHP) 132.\(^8\) For
tetrahydropyran 131, initially a Petasis-Ferrier union/rearrangement\textsuperscript{93,94} was explored, an approach which has been implemented in several total syntheses published by the Smith group.\textsuperscript{95-97} Formation of dioxanone 137 from \(\beta\)-hydroxy acid 135 and aldehyde 136 was readily accomplished in near quantitative yield by employing TMSOTf as a Lewis acid (Scheme 3.2).\textsuperscript{98} Despite the success of the Petasis-Ferrier union/rearrangement, in which ketone 138 was prepared in 56\% yield from dioxanone 137, subsequent installation of the C25 stereocenter in a selective manner could not be realized.   

**Scheme 3.2.** Petasis-Ferrier union/rearrangement approach to THP 131.

Unable to install the C25 alcohol in a stereoselective fashion, they turned their attention towards an aldol approach for the preparation of tetrahydropyran 131. Toward this end, ketone 140 and aldehyde 141 were prepared and utilized in a boron-mediated aldol reaction, giving rise to \(\beta\)-hydroxy ketone 142 in 93\% yield as a separable mixture of diastereomers (Scheme 3.3). Each diastereomer was subjected to acidic conditions to cleave the triethylsilyl (TES) ether and induce formation of mixed methyl ketal 143 or 144 in 82\% or 92\% yield, respectively. At this point, the moderate selectivity of the aldol
reaction could be addressed, as the minor diastereomer could be converted to 143 by means of a high yielding oxidation-reduction sequence.

**Scheme 3.3.** Aldol approach to tetrahydropyran 131.

Introduction of the C16-C18 fragment to alkyne 143 was the next task at hand. The reduction of mixed methyl ketal 143 by triethylsilane mediated by TMSOTf, followed by protection of the C25 alcohol as the methoxymethyl (MOM) ether delivered tetrahydropyran 145 in 93% yield over the two steps (Scheme 3.4). Alkyne 145 was converted to an intermediate vinyl iodide via a hydrozirconation/iodination sequence. Suzuki-Miyaura coupling with alkyl boronate 146 generated the carbon skeleton of the C16-C29 fragment in quantitative yield over the two steps. Protecting group manipulation of tetrahydropyran 147 generated alcohol 148 in 59% yield over the three steps. Finally, conversion of the alcohol to the sulfone under standard conditions afforded tetrahydropyran 131 in 17 steps and 17% overall yield.
Scheme 3.4. Synthesis of tetrahydropyran 131.

Their approach toward the dihydropyran fragment hinged on the success of a conjugate addition/α-oxidation sequence with dihydropyranone 150 and vinyl bromide 155 (Scheme 3.5). The requisite dihydropyranone was prepared via a hetero Diels-Alder reaction between the Danishefsky diene and aldehyde 149, available from 1,3-propanediol in two steps. The hetero Diels-Alder reaction proceeded with both high yield and enantioselectivity (20:1 er) in the presence of a catalytic amount of chromium (III) complex 151, initially developed by Jacobsen. Vinyl bromide 155 was prepared in five steps, with the lone stereocenter installed via a Myers alkylation with ephedrine-derived auxiliary 152.
Upon generation of the higher order cuprate derived from vinyl bromide 155 and addition of dihydropyron 150, the enolate formed in situ was trapped as the silyl enol ether to give rise to 156 in 61% yield (Scheme 3.6). Rubottom oxidation\textsuperscript{104} and protection of the resultant alcohol as the TBS ether provided α-hydroxy ketone 157 in 46% yield over the three steps. Formation of the vinyl triflate\textsuperscript{105} derived from the kinetic enolate, followed by reduction\textsuperscript{106} afforded dihydropyran 158 in 71% yield. The alcohol at C1 was converted to the tert-butyl ester upon cleavage of the p-methoxybenzyl ether followed by a three step oxidation sequence to deliver tert-butyl ester 160.\textsuperscript{107} As a result of the ambiguous representation of the C10 stereocenter, Smith and co-workers initially targeted ester 160 in their efforts towards sorangicin A, in which the C10 stereocenter is inverted. Upon confirmation of the C10 stereochemistry by Jansen, ester 160 was converted to dihydropyran 162 by a five step sequence. Unfortunately, attempts to correct the stereochemistry by means of a Mitsunobu reaction were met with failure due to the predominance of the S\textsubscript{N}2´ pathway. Upon inversion of the C10 stereocenter,
cleavage of the primary TBS ether from dihydropyran 162 and conversion of the alcohol to sulfone 132 was accomplished using standard conditions in 70% yield over the three steps. This route developed by Smith and coworkers enables the preparation of the dihydropyran fragment, sulfone 132, in 25 steps and 4.0% overall yield.


A route towards the final fragment, dioxabicyclo[3.2.1]octane core 133, was first reported by Smith in 2004. Their synthesis featured a kinetically controlled, regio- and stereoselective epoxide ring opening to arrive at the desired fragment in 15 steps and 2.4% overall yield. The lessons learned from their synthesis of the dihydropyran led to
the publication of a second generation synthesis of bicyclic aldehyde 133 in 2009.\textsuperscript{108} The revised approach was more efficient both in terms of number of steps and overall yield than the original route.

The second generation route towards bicyclic ether 133 begins with a hetero Diels-Alder reaction between the Danishefsky diene and aldehyde 163 in the presence of previously used chromium-Schiff base 151.\textsuperscript{109} Under these conditions, dihydropyrone 164 was prepared in 86\% yield and a 33:1 diastereomeric ratio (Scheme 3.7). Conjugate addition followed by trapping of the \textit{in situ} generated enolate was explored. Bromostyrene was selected as a suitable nucleophile, wherein the styrene component would serve as a masked aldehyde. Lithium halogen exchange of the bromine with \textit{tert}-butyllithium followed by addition of dimethylzinc and subsequent addition to dihydropyrone 164 effected the desired conjugate addition.\textsuperscript{110} Quenching of the enolate with methyl iodide in the presence of HMPA led to the desired product, albeit in a moderate 51\% yield. Further optimization of this reaction revealed that addition of CuI-PBu\textsubscript{3} prior to addition of methyl iodide attenuated the reactivity of the zinc enolate, allowing for formation of ketone 165 in 73\% yield. Selective reduction of the ketone with L-selectride followed by cleavage of the acetonide revealed triol 166 in 80\% yield. The triol could be converted to bicyclic ether 168, an intermediate from our synthesis of the C29-C37 bicyclic ether fragment, directly upon addition of potassium hexamethydisilazide and trisyl chloride in 33\% yield. Alternatively, a two-step protocol involving selective sulfonylation of the primary hydroxyl followed by treatment with KHMDS, furnished 168 in a much improved 70\% yield over the two steps. Parikh-Doering oxidation\textsuperscript{111} of the resultant alcohol and subsequent Takai olefination\textsuperscript{112,113} delivered the E- and Z-vinyl iodides in 52\% and 16\% yields, respectively. Finally, chemoselective dihydroxylation of the electron rich olefin followed by oxidative cleavage
of the diol generated bicyclic aldehyde 133 in 10 steps from aldehyde 163 and 11.3% overall yield.

Scheme 3.7. Synthesis of bicyclic aldehyde 133.

In this publication, Smith and co-workers also demonstrated the viability of the proposed Stille coupling for installing the (Z,Z,E)-trienoate (Scheme 3.8). The palladium catalyzed reaction between vinyl iodide 133 and vinyl stannane 134 furnished trienoate 170 in 96% yield, which upon treatment with lithium hydroxide, could be converted to acid 171. Most notably, these conditions delivered the acid with complete preservation of the olefin geometry.

Scheme 3.8. Stille coupling to install the (Z,Z,E)-trienoate.
With the three key fragments in hand, and precedent for the installation of the sensitive trienoate moiety, investigation of the Julia-Kocienski olefination$^{114}$ for forming the C15-C16 and C28-C29 bonds was the next task at hand. Development of conditions for the union of tetrahydropyran 131 and bicyclic aldehyde 133 was not trivial (Scheme 3.9). Investigation of several different solvent and base combinations revealed that tert-butyl lithium in a 3:1 ratio of DMF and HMPA provided the best yields of coupled adduct 172, as exclusively the $E$-olefin.$^{115}$ Several recycles of the recovered starting material allowed for the advancement of the coupled material in around 65% yield. In two steps, C1-C38 fragment 172 was converted to aldehyde 173, setting up the second Julia-Kocienski reaction. They were pleased to find that the second key fragment coupling between sulfone 132 and aldehyde 173 proceeded in 88% yield with complete conversion and olefin selectivity when the reaction was run in DME with KHMDS as the base.

At this point, all that remained was installation of the C39-C43 trienoate and global deprotection. After cleavage of the C25 TBS ether from the C1-C38 fragment 174, a Stille coupling with vinyl stannane 134 was achieved in 88% yield using the conditions from the model system (Scheme 3.10). The excess Ph₂PO₂NBu₄ suppressed E/Z isomerization allowing for the isolation of (Z,Z,E)-trienoate 175 with minimal isomerization. Hydrolysis of the ester was quickly followed by macrolactonization using the Evans-modified Mukaiyama protocol to deliver macrocycle 177, containing the entire carbon skeleton of the natural product. Identification of conditions for the global deprotection was nontrivial, as it was known that the (Z,Z,E)-trienoate was extremely sensitive to isomerization. Thus, mild conditions which effected the cleavage of the methoxymethyl ether, acetonide, and tert-butyl protecting groups were eventually realized after a considerable amount of experimentation, to deliver (+)-sorangicin A (130) in 70% yield over the final two steps.
ii. Schinzer’s synthesis of the C8-C15, C21-C28, and C29-C37 fragments

Besides the total synthesis by Smith and co-workers, the Schinzer group has reported the most progress towards the natural product. Their retrosynthetic approach involves a similar disconnection strategy to that employed by Smith, in which they would target tetrahydropyran 178, bicyclic ether 179, dihydropyran 180, and alcohol 181 (Scheme 3.11). In 2004, Schinzer and co-workers published their approach towards each of these orthogonally functionalized fragments, although no indication of their coupling strategy was divulged in this paper, and no progress has since been reported.
A key feature of their synthetic approach is exploitation of the similar structures of the bicyclic ether and tetrahydropyran (THP) portions of the natural product. These fragments differ only in the stereochemistry at C27 and C31 allowing for the preparation of tetrahydropyran (THP) 178 and bicyclic ether 179 from a common starting material (Scheme 3.12). Beginning with aldehyde 149, also utilized as a starting material in Smith's synthesis of the dihydropyran, asymmetric crotylation 120 followed by protection of the resultant alcohol as the TIPS ether generated terminal olefin 183 in 60% yield over the two steps. Osmium tetraoxide mediated dihydroxylation delivered a mixture of 1,2-diols 184 and 185 in 48% and 24% yield, respectively. Upon separation of the diastereomers, diol 184 was taken on to bicyclic ether 179, while diol 185 was advanced to tetrahydropyran 178.

Efforts were first directed towards the synthesis of tetrahydropyran 178 from diol 185, the minor diastereomer from the dihydroxylation reaction. Protection of diol 185 as the acetonide with concurrent cleavage of the primary TBS ether, followed by TPAP oxidation furnished aldehyde 186 in 62% yield over the two steps (Scheme 3.13). Homologation of the aldehyde to Z-α,β-unsaturated ester 187 was accomplished via a Horner-Wadsworth-Emmons olefination with the Still-Gennari reagent in 91% yield. A three step reduction, epoxidation, and protection sequence afforded benzyl ether 188 in 44% yield over the three steps. Finally, exposure of epoxide 188 to CSA effected formation of tetrahydropyran 178 via a ring closing–epoxide opening cascade.


Diol 184 was carried through the identical seven step sequence to deliver tetrahydropyran 189 in 16% yield (Scheme 3.14). In order to convert tetrahydropyran to the desired bicyclic ether, several steps of protecting group manipulations were carried out to give rise to alcohol 190 in 49% yield over the four step sequence. Upon treatment of secondary alcohol 190 with mesyl chloride, a 59% yield of mesylate 191, along with 28% of the desired bicyclic ether 179 were obtained. From the mesylate, bicyclic ether 179 could be accessed in 45% yield over two additional steps via removal of the p-methoxybenzyl ether and treatment with base. This synthetic approach, which takes advantage of the similarities between the THP and bicyclic ether fragments, allowed for
the preparation of THP 178 in 10 steps and 6% overall yield and bicyclic ether 179 in 17 steps and less than 1% overall yield.

**Scheme 3.14.** Synthesis of bicyclic ether 179.

For the remaining dihydropyran subunit, Schinzer and co-workers opted to use a starting material from the chiral pool, namely L-glucose, which bears the requisite stereochemistry at C9 and C10 (Scheme 3.15). From L-glucose (192), a known one-pot, three-step procedure developed by Koreeda\(^{123}\) was employed to prepare a tri-O-acetyl-L-glucal, which upon deprotection yielded dihydropyran 193 in 81% yield over the two steps. Treatment of triol 193 with allyltrimethyl silane and TMSOTf delivered allylated product 194 in 84% yield with excellent diastereoselectivity (>99%). Protection of diol 194 as the bis-TBS ether followed by chemoselective cleavage of the terminal olefin generated aldehyde 195 in 70% yield. The aldehyde was converted to the dimethyl acetal and the primary TBS ether was selectively cleaved to give rise to acetal 196 in 69% yield over the two steps. Finally, the C8 methyl ketone was installed by a three-step oxidation, Grignard addition, oxidation sequence in 78% yield, completing C8-C15 fragment 180 in 10 steps and 25.5% overall yield. Efforts by the Schinzer group to couple these key fragments and complete the total synthesis are currently underway.
iii. Lee’s synthesis of the C8-C15 fragment

The Lee group has reported two pathways for accessing C8-C15 dihydropyran 203, both of which utilize a ring-closing metathesis for assembly of the six-membered ring. The first route features the aldol/ring closing metathesis approach which was developed in our laboratories for the preparation of medium ring ethers (Scheme 3.16). Beginning with allylic alcohol 197, initial treatment with bromoacetic acid gave rise to glycolic acid 198 in near quantitative yield. Conversion of the acid to the mixed anhydride followed by addition of lithiated oxazolidinone 199 delivered acylated product 200 in 81% yield. An aldol reaction between glycolate 200 and acrolein provided aldol adduct 201 in 73% yield with excellent diastereoselectivity (93:7 dr). Protection of the resultant secondary alcohol as the TBS ether followed by lithium borohydride reduction afforded diene 202 in 80% yield over the two steps. Formation of the six-membered ring was realized upon treatment of diene 202 with Grubbs 1st generation catalyst (G1), generating C8-C15 dihydropyran 203 in 86% yield. The aldol/ring closing metathesis approach provided C8-C15 dihydropyran 203 in six steps and 40% overall yield.
The Lee group also investigated a more novel approach towards C8-C15 dihydropyran 203 which features an enantioselective rhodium catalyzed allylic etherification reaction (Scheme 3.17).126,127 This route towards the desired intermediate commences with an Evans syn aldol reaction between p-methoxybenzyl glycolate 204 and acrolein, to generate aldol adduct 205 in 84% yield in a 92:8 diastereomeric ratio. A four step sequence converted aldol adduct 205 to bis-TBS alcohol 207 in 70% yield. The Rh-catalyzed allylic etherification reaction between homoallylic alcohol 207 and tert-butyl carbonate 208 afforded diene 209 in 67% yield. Upon removal of the primary TBS ether and ring-closing metathesis, previously prepared dihydropyran 203 was obtained in eight steps and 26% overall yield.
iv. Srihari’s synthesis of the C16-C29 fragment

The Srihari group recently reported a Prins cyclization approach towards C16-C28 fragment 148, an intermediate from Smith’s total synthesis of (+)-sorangicin A. The carbohydrate-based approach begins with opening of lactol 210, available in one step from D-ribose (Scheme 3.18). The treatment of lactol 210 under Wittig conditions effected opening of the lactol with concurrent methylene Wittig olefination to deliver terminal olefin 211. The primary alcohol was converted to the tosylate in the presence of dibutyltin oxide; subsequent treatment of the tosylate with sodium hydride resulted in formation of epoxide 212 in 61% yield from acetonide 210. Upon addition of lithiated propyne to epoxide 212, an intermediate alkyne was generated, which after Lindlar reduction delivered Prins cyclization precursor 213 in 97% yield.
With cyclization precursor 213 in hand, formation of the tetrahydropyran by a Prins cyclization was explored. Initially, a Prins cyclization between homoallylic alcohol 213 and 3-benzyloxy propionaldehyde was investigated. Unfortunately, under these conditions, none of the cyclized product was obtained; thus, a segment coupled Prins cyclization with α-acetoxy ether 215 was pursued (Scheme 3.19). Esterification of alcohol 213 with 3-benzyloxy propanoic acid in the presence of DCC, followed by reduction and acetate formation, afforded cyclization precursor 387 in 98% yield. The treatment of α-acetoxy ether 215 with boron trifluoride diethyl etherate and acetic acid initiated the Prins cyclization to give rise to tetrahydrofuran 216 as a 9:1 mixture of diastereomers, epimeric at the C26 methyl group. Fortuitously, the major product featured the necessary stereochemistry at the methyl position; unfortunately, the same was not true for the C25 alcohol, also formed during the Prins cyclization. Upon cleavage of the acetate followed by oxidation to ketone 217, several conditions for the selective introduction of the C25 alcohol were explored. Disappointingly, all attempts resulted in a separable 1:1 mixture of diastereomers. The best yields were obtained with di-iso-butylaluminum hydride, which gave rise to a 1:1 diastereomeric mixture of alcohols.
218a and 218b in 46% and 50% yield, respectively. The diastereomers were separated and only alcohol 218a, bearing the appropriate stereochemistry at C25, was carried forward. A cross metathesis with TBS-protected 4-pentenol was envisioned for installation of the C16-C19 fragment. Initial attempts were made to effect the cross metathesis in the presence of the acetonide protecting group; however, disappointing results prompted them to remove the acetonide protecting group prior to the cross metathesis reaction. Toward this end, after protection of the C25 alcohol as the methoxymethyl ether, the acetonide was exposed to strongly acidic conditions to reveal diol 219 in 88% yield over the two steps. The subsequent cross metathesis reaction between TBS protected 4-pentenol and diol 219 proceeded in 65% yield.6d With cross metathesis adduct 220 in hand, access to Smith’s C16-C28 intermediate 148 was attained upon re-protection of the cross metathesis adduct as the acetonide and cleavage of the benzyl ether. This route described by Srihari enables the preparation of Smith’s C16-C28 intermediate in 17 steps and 7.7% overall yield from D-ribose.
Mohapatra’s synthesis of the C30-C37 bicyclic ether

The most recent publication regarding the synthesis of (+)-sorangicin A was published by Mohapatra and co-workers, detailing the implementation of methodology developed in their group for accessing trans-2,6-disubstituted-3,4-dihydropyrans from α,β-unsaturated aldehydes. This novel iodine-catalyzed reaction for the preparation of dihydropyrans in a highly diastereoselective manner was applied toward the synthesis of the signature C30-C37 bicyclic ether core.

Unsaturated aldehyde 221, available from benzylxyacetaldehyde in two steps via an asymmetric crotylation, cross metathesis sequence was exposed to allyl
trimethyl silane and iodine to form \textit{trans}-2,6-disubstituted-3,4-dihydropyran 222 in 90\% yield (Scheme 3.20). A two step oxidative cleavage of the terminal olefin delivered aldehyde 223 in 80\% yield. Asymmetric $\alpha$-aminoxylation, with proline as the catalyst and nitrosobenzene as the oxygen source, followed by \textit{in situ} sodium borohydride reduction gave rise to 1,2-diol 224 in 61\% yield.\textsuperscript{133,134} The primary alcohol was selectively protected as the \textit{tert}-butyldiphenylsilyl (TBDPS) ether and subsequently treated with $N$-iodosuccinimide to furnish iodo-ether 225 as the only regioisomer. Finally, reduction with azobis-\textit{iso}-butyronitrile (AIBN) and tributyltin hydride afforded C30-C37 bicyclic ether 226 in 95\% yield, and 21\% overall yield for the eight step sequence.

\textbf{Scheme 3.20.} Mohapatra's synthesis of the C30-C37 bicyclic ether core.
CHAPTER FOUR

Formal Synthesis of the C1-C38 Fragment of (+)-Sorangicin A

4.1 Synthetic approach towards (+)-sorangicin A

As in the previously reported approaches towards (+)-sorangicin A (130), we sought to divide the molecule into three key fragments: bicyclic ether 227, tetrahydropyran 228, and dihydropyran 229. It was envisioned that the preparation of these orthogonally differentiated fragments would allow us to investigate several coupling strategies (Scheme 4.1). Our initial focus was devoted to the development of efficient and high-yielding routes towards each of the core synthetic fragments.

Scheme 4.1. Synthetic approach towards (+)-sorangicin A: core synthetic fragments.
4.2 Synthesis of the Core Fragments

i. Synthesis of bicyclic ether 227

Our synthetic approach towards bicyclic ether 227 by was reported by Crimmins and Haley in 2006.87,135 The route features an epoxide opening cascade with epoxy tosylate 236 to form the unique dioxabicyclo[3.2.1]octane skeleton. The synthesis of cyclization precursor 236 commenced with an anti-aldol reaction between N-propionylthiazolidinethione 230 and cinnamaldehyde (Scheme 4.2).136 The resultant alcohol was protected in situ as the trimethylsilyl (TMS) ether to afford the protected aldol adduct in one step. Reductive removal of the chiral auxiliary with di-iso-butylaluminum hydride furnished aldehyde 231 in 63% yield over the two steps. Aldehyde 231 was subsequently employed in an asymmetric Brown allylation with (+)-B-allyldiisopinocampheyl borane to deliver diol 232 in 90% yield and excellent diastereoselectivity (>95:5 dr).137 Formation of p-methoxyphenyl (PMP) acetal 233 was achieved upon exposure of diol 232 to 4-methoxybenzaldehyde dimethyl acetal and PPTS. Homologation of the carbon backbone by a cross metathesis reaction between ethyl acrylate and PMP-acetal 233 delivered an intermediate α,β-unsaturated ester,64 which upon di-iso-butylaluminum hydride reduction gave rise to allylic alcohol 234 in 88% yield over the two steps. The selection of a cyclic acetal for protection of the diol was critical, as the six-membered ring fixes the olefin side chains into a bis-equatorial relationship, such that ring closing metathesis is strongly disfavored. The conversion of allylic alcohol 234 to the requisite epoxide was accomplished via a Sharpless asymmetric epoxidation138 to deliver epoxide 235 in 83% yield as a single diastereomer. Epoxide 235 was swiftly converted to the cyclization precursor, epoxy tosylate 236, in 85% yield under standard conditions.
With epoxy tosylate 236 in hand, the epoxide opening cascade to form the signature bicyclic ether was explored (Scheme 4.3). Initially, a stepwise approach towards bicyclic ether 227 was investigated in which treatment of epoxy tosylate 236 with 5% HCl in THF/methanol facilitated cleavage of the p-methoxyphenyl (PMP) acetal and opening of the epoxide with concomitant formation of tetrahydropyran 237.\textsuperscript{139,140} While the option for formation of a 5-membered tetrahydrofuran by a 5-endo-ring closure was possible, it was expected that the 6-exo-cyclization to form tetrahydropyran 406 would be favored due to better overall orbital overlap.\textsuperscript{141} Next, tetrahydropyran 237 was exposed to potassium carbonate in methanol which upon displacement of the tosylate triggered rapid formation of epoxide 238. Attempts to purify epoxide 238 resulted in decomposition; alternatively, the crude epoxide could be treated directly with 5% HCl in THF/MeOH to initiate the 5-exo-cyclization/epoxide opening cascade, generating bicyclic ether 227 in 84% yield over the two steps. Upon further experimentation, Haley determined that this three step sequence could be accomplished in a more convenient
one-pot procedure in approximately the same overall yield. The one-pot procedure was achieved by first treating epoxy tosylate 236 with 10% HCl in THF/methanol. Upon consumption of the starting material, as observed by thin layer chromatography (TLC), 10% aqueous NaOH was added until the reaction was basic. The conversion of tetrahydrofuran 237 to epoxide 238 occurred immediately, at which time the reaction mixture was acidified with a second portion of 10% HCl. The three step, one-pot procedure afforded bicyclic ether 227 in 62% yield, essentially the same as the 63% overall yield obtained for the stepwise procedure. This synthetic approach, which features a regioselective epoxide opening cascade to form both rings of the bicyclic ether, provided the C29-C37 fragment of sorangicin A in nine steps and 16% overall yield.

**Scheme 4.3.** One-pot vs. stepwise approach to bicyclic ether 227.

### ii. **Synthesis of tetrahydropyran 228**

Attention was then turned to the synthesis of tetrahydropyran 228. As evidenced by Schinzer’s approach to the bicyclic ether and tetrahydropyran fragments, these cyclic ethers are structurally very similar. Schinzer exploited this similarity by preparing both of these fragments from a common intermediate. Comparison of tetrahydropyran 228 to
THP-diol 237, an intermediate from the epoxide-opening cascade to form bicyclic ether 227, reveals that these intermediates differ only in the orientation about two stereocenters (Scheme 4.4). Crimmins and Haley intended to take advantage of this relationship by using a sequence analogous to that employed for the synthesis of bicyclic ether 227 to access tetrahydropyran 228. As bicyclic ether 227 was derived from epoxy tosylate 236, tetrahydropyran 228 would arise from epoxide 239, which would serve as the cyclization precursor.

**Scheme 4.4. Similarity of the bicyclic ether and tetrahydropyran fragments.**

The synthesis of tetrahydropyran 228 began with an Evans syn aldol addition between N-propionylthiazolidinethione 63 and 3-butenal51 to deliver the aldol adduct in 95% yield (Scheme 4.5). The resultant secondary alcohol was protected as the TBS ether to furnish protected aldol adduct 240 in 98% yield. Elongation of the carbon backbone was achieved by a cross metathesis with ethyl acrylate to afford α,β-unsaturated ester 241 in 88% yield. The treatment of cross metathesis adduct 241 with approximately six equivalents of di-iso-butylaluminum hydride effected reduction of the α,β-unsaturated ester, while also cleaving the thiazolidinethione auxiliary. The resultant alcohol was protected as the acetate to furnish aldehyde 242 in 68% yield over the two
steps. Subsequent Brown asymmetric allylation\textsuperscript{137} of aldehyde 242 with (+)-Ipc\textsubscript{2}B-allyl gave rise to diol 243 in 77% yield after basic workup.

\textbf{Scheme 4.5.} Synthesis of cyclization precursor 243.

As in the synthesis of the bicyclic ether fragment, cyclization to form the 6-membered tetrahydropyran would be facilitated by treatment of the corresponding epoxy alcohol 239 with acid. It was postulated that by utilizing an acidic workup for the Sharpless asymmetric epoxidation,\textsuperscript{138} tetrahydropyran 244 could be prepared directly from allylic alcohol 243 by a 6-exo-cyclization of intermediate epoxy alcohol 239 (Scheme 4.6). In this case, the opportunity to form a seven-membered cyclic ether by a 7-endo-ring closure exists; however, the 6-exo-cyclization to form the desired tetrahydropyran was expected to be highly favored. This proved to be the case as upon acidic workup of the Sharpless asymmetric epoxidation, tetrahydropyran 244 was obtained in 82% yield. Protection of the diol as the bis-TES ether afforded tetrahydropyran 228 in 90% yield. This route towards the tetrahydropyran fragment, which parallels our approach towards bicyclic ether 227, delivered tetrahydropyran 228 in eight steps and 32% overall yield.
With bicyclic ether 227 and tetrahydropyran 228 in hand, we shifted our focus towards the synthesis of the remaining core fragment, dihydropyran 229. Due to the unsaturation of the 6-membered ring, dihydropyran 229 required a significantly different approach than the acid-catalyzed epoxide-opening cascade employed for the previous two fragments. With inspiration from the aldol/ring closing metathesis approach to medium ring ethers developed in our group, it was envisioned that dihydropyran 229 could be prepared in a similar fashion through an alkoxy-allylation/ring closing metathesis sequence.

The synthesis of dihydropyran 229 began with aldehyde 154, also utilized by Smith en route to vinyl bromide 155, which was employed in their synthesis of the dihydropyran fragment (Scheme 4.7). A Wittig olefination with stabilized ylide installed the requisite tri-substituted olefin, giving rise to an intermediate α,β-unsaturated ester. After a reduction, oxidation sequence, α,β-unsaturated aldehyde 246 was obtained in 78% yield over the three steps. Aldehyde 246 was converted to differentially protected syn-1,2-diol 247 via a Brown asymmetric alkoxyallylation with the [(Z)-γ-
alkoxyallyl]diisopinocampheyl borane generated in situ from methoxymethyl allyl ether and (+)-B-methoxydiisopinocampheyl borane.\textsuperscript{143} The conversion of the resultant secondary alcohol to diene 248 was accomplished in 87% yield by subjecting allylation adduct 247 to a catalytic amount of PPTS in neat acrolein diethyl acetal.\textsuperscript{144} With diene 248 in hand, conditions for the ring closing metathesis to form the dihydropyran were explored.\textsuperscript{37} Initial attempts at the ring closing metathesis were plagued by low conversion and inconsistent yields. After screening a number of conditions, Haley determined that running the reaction in refluxing methylene chloride (0.015 M) in the presence of 10 mol % Grubbs 2\textsuperscript{nd} generation catalyst provided the most consistent results, to give rise to cyclized product 249 in 59% yield as an inconsequential mixture of diastereomers. We later determined that the yield for the ring closing metathesis could be improved to 83% by running the reaction in toluene at 80 °C at a slightly more dilute concentration (0.01 M). Installation of the allyl side chain was accomplished by a Sakurai reaction with mixed acetal 249 and allyltrimethyl silane to deliver trans-2,6-disubstituted-3,4-dihydropyran 250 in 92% yield as a single diastereomer.
The Sakurai reaction proceeds through an $S_{N}1$ pathway, in which two possible oxocarbenium transition states can be accessed (conformer A or B) upon treatment of mixed acetal 249 with Lewis acid (Scheme 4.8).\textsuperscript{145,146} The excellent diastereoselectivity for dihydropyran 250 is rationalized by well precedented pseudoaxial addition to the more populated oxocarbenium conformer B from the top face (path C). Conformer B is the favored transition state due to the minimization of steric interactions as a result of the large alkyl substituent ($R_L$) occupying an equatorial orientation and the lone pair stabilization provided by the axially oriented methoxymethyl (MOM) ether, which is not available in conformer A. Addition from the bottom face of conformer A (path B) is highly disfavored as a result of the developing syn-pentane interaction between the large alkyl substituent ($R_L$) and the allyl group in the product. A similar steric interaction would result between the allyl group and the MOM ether upon nucleophilic addition to the bottom face of conformer B (path D), making path C, which delivers the product with the requisite stereochemistry at C13, the most favorable pathway for addition to the
oxocarbenium ion. The stereochemical outcome of the Sakurai reaction with mixed acetal 249 was confirmed by 2-D NOESY NMR analysis. A strong correlation between the proton at C9 with the proton at C10 and the protons of the allyl side chain was observed, while the absence of a cross peak between the protons at C9 and C13 confirmed the stereochemical assignment of dihydropyran 250 as the 2,6-trans product.

**Scheme 4.8.** Model for the Diastereoselectivity of the Sakurai reaction with mixed acetal 249.

Introduction of the desired oxidation state of C1 was achieved by an analogous four step sequence to that employed by Smith and co-workers in their synthesis of the dihydropyran fragment (Scheme 4.9). Cleavage of the PMB ether from dihydropyran 250 under oxidative conditions with DDQ delivered alcohol 251 in 83% yield. A Dess-Martin oxidation gave rise to aldehyde 252, which after a Pinnick oxidation to the intermediate acid, was swiftly converted to tert-butyl ester 229 upon treatment of the crude acid with tert-butyl isourea. This sequence provided dihydropyran 229 in 11 steps from aldehyde 154 and 22% overall yield.
4.3 Cross metathesis approach toward assembly of the natural product

Upon development of synthetic routes towards each of the core fragments, assembly of the natural product was the next task at hand. A distinct advantage of the modular approach developed by Haley and Crimmins towards bicyclic ether 227, tetrahydropyran 228, and dihydropyran 229 is the opportunity to investigate a number of coupling strategies with only slight modification of these key intermediates.

Haley quickly determined that a cross metathesis reaction was a viable approach towards uniting the elaborated bicyclic ether and tetrahydropyran fragments; however, the design of a consistent and high yielding approach for introducing the dihydropyran moiety proved to be a considerable challenge (Figure 4.1).\(^\text{135}\) The absence of the C16-C20 fragment from the three key intermediates provides additional flexibility, such that introduction of the dihydropyran could be achieved via formation of either the C20-C21, C19-C20, or C15-C16 bond. Both the acetylide addition to form the C20-C21 bond and the vinylzinc addition/cross metathesis approach to form the C19-C20 bond were investigated by Haley, and provided disappointing results. We were pleased to find that the cross metathesis reaction to form the C15-C16 bond gave rise to the coupled
adduct; therefore, we decided to pursue a cross metathesis approach to unite the three core synthetic fragments.

![Figure 4.1. Possible disconnections for the assembly of sorangicin A.](image)

Retrosynthetically, we envisioned using a similar endgame strategy to Smith, in that the C39-C43 trienoate would be installed at a late stage by a Stille coupling between the vinyl iodide derived from C1-C37 fragment 253 and vinyl stannane 134 (Scheme 4.10). We sought to prepare advanced C1-C37 intermediate 253 by a cross metathesis reaction between dihydropyran 229 and bicyclic ether/THP fragment 254. Bicyclic ether/THP fragment 254 was envisioned arise from a cross metathesis reaction with protected bicyclic ether 255 and tetrahydropyran 256, to which the C16-C20 fragment has been incorporated.
i. **Cross metathesis to form the C29-C30 bond**

Efforts towards bicyclic ether/THP fragment 254 began with preparation of cross metathesis partner 255, available from bicyclic ether 227 via a three step sequence (Scheme 4.11). The protection of the alcohol of bicyclic ether 227 as the pivalate proceeded in 91% yield. Next, a two step ozonolysis, methylene Wittig sequence was employed to convert the styrene component to the terminal olefin, thus giving rise to cross metathesis partner 255 in 90% yield over the two steps.\(^{135}\)
Attention was then turned to incorporation of the C16-C20 fragment to tetrahydropyran 228. The conversion of tetrahydropyran 228 to aldehyde 258 was realized upon subjection of bis-TES ether 258 to modified Swern conditions which are known to convert primary TMS and TES ethers directly to the aldehyde in the presence of secondary silyl ethers (Scheme 4.12). The vinylzinc species, generated in situ from C16-C20 vinyl iodide 259, underwent a Felkin-Anh controlled addition to aldehyde 258 to give rise to alcohol 260 in 68% yield as an 8:1 mixture of diastereomers. Subsequent conversion of the vinyl addition product to the acetonide by a two step sequence afforded dihydropyran 256 in 93% yield. The configuration of the major product as the desired diastereomer was confirmed by 2-D NMR analysis.

With both bicyclic ether 255 and acetonide 256 in hand, cross metathesis to form the C29-C30 bond was explored. Initial cross metathesis attempts were plagued by low
yields due to dimerization of the tetrahydropyran fragment; conversely, unreacted bicyclic ether 255 could be recovered cleanly from the reaction mixture (Scheme 4.13). In order to minimize consumption of the starting material by dimerization, the tetrahydropyran was added via syringe pump over several hours to a solution of bicyclic ether 255 and Grubbs 2nd generation catalyst (G2) in refluxing methylene chloride. Under these conditions, cross metathesis adduct 261 was obtained in 40% yield, with 55% of bicyclic ether 255 recovered unreacted.\textsuperscript{135} Despite the moderate yield obtained for the first coupling reaction, cross metathesis adduct 261 was advanced to terminal olefin 254 to assess the viability of the second cross metathesis with dihydropyran 229. Due to the presence of the tert-butyl ester in the dihydropyran fragment, cleavage of the pivalate ester was necessary. The treatment of cross metathesis adduct 261 with di-iso-butylaluminum hydride reduced the pivalate ester to afford alcohol 262 in 88% yield. Removal of the TIPS protecting group, followed by hydrogenation of the alkyne in the presence of Lindlar’s catalyst,\textsuperscript{151} gave rise to terminal olefin 254 in 74% yield over the two steps.
Cross metathesis to form the C15-C16 bond

Having developed a convergent route toward bicyclic ether/THP fragment 254, focus was shifted to formation of the C15-C16 via cross metathesis. Initial attempts by Haley to unite bicyclic ether/THP fragment 254 and dihydropyran 229 were met with some success (Scheme 4.14). Cross metathesis adduct 253 was obtained in 30-40% yield when the reaction was run in the presence of Hoveyda-Grubbs 2\textsuperscript{nd} generation catalyst (HG2); however, unreacted alcohol 254 and dihydropyran 229 were only recovered in approximately 30% yield as a mixture with their homodimers. Despite the poor conversion and mass recovery, we opted to pursue this route further. We speculated that the low conversion could be attributed to the fact that these coupling reactions were conducted on a very small scale.
4.4 Optimization of the route towards the C16-C37 fragment

In light of the promising results obtained for cross metathesis reactions to form the C29-C30 and C15-C16 bonds, my initial focus was optimization of the yield for both of these major bond forming events. In addition, we were also interested in revising our protecting group strategy. It has been reported that sorangicin A is unstable to a number of reagents, including fluoride sources, which are often utilized for the cleavage of silyl ethers. Insight gained from the total synthesis completed by Smith and co-workers suggested that exchange of several of our protecting groups early in the synthesis could prevent late stage protecting group compatibility issues. As a result, we decided to employ an identical protecting group strategy to that successfully used by Smith in the only total synthesis of (+)-sorangicin A to date.

i. Modification of the protecting group strategy

We opted to modify the protecting groups on the bicyclic ether and tetrahydropyran fragments prior to optimization of the coupling reaction, as even a minor change in the cross metathesis substrate can have an effect on the outcome of the reaction. Turning our attention to the bicyclic ether fragment, we were interested in preparing p-methoxybenzyl (PMB) protected bicyclic ether 264 instead of pivalate 255.
Thus, bicyclic ether 227, the product of the epoxide opening cascade, was treated with \(p\)-methoxybenzyl bromide and sodium hydride to give rise to PMB-protected bicyclic ether 263 in 94% yield (Scheme 4.15). As a consequence of this protecting group modification, ozonolysis could no longer be employed for cleavage of the carbon-carbon double bond. Instead, the Johnson-Lemieux protocol\(^{152}\) was called upon to convert the styrene component to an intermediate aldehyde by a one-pot dihydroxylation, oxidative cleavage sequence. Subsequent methylene Wittig olefination\(^{63}\) delivered bicyclic ether 264 in 87% yield over the two steps.

Next, we wanted to replace the TBS ether of tetrahydropyran 228 with a methoxymethyl (MOM) ether in order to parallel the protecting group strategy employed by Smith. This protecting group modification could be achieved by either a deprotection/protection sequence with tetrahydropyran 228 or introduction of the MOM ether at the beginning of the tetrahydropyran synthesis. It was quickly realized that protecting group manipulation of tetrahydropyran 228 would not deliver the desired MOM-protected tetrahydropyran (Scheme 4.16). We had envisioned that after removal of the three silyl ethers from tetrahydropyran 228, we could selectively protect the C21 and C22 alcohols as triethylsilyl ethers; subsequent formation of the C25 MOM ether would give rise to the desired tetrahydropyran fragment. Upon treatment of tetrahydropyran 228 with several equivalents of TBAF, diol 265, with the C25 TBS ether still intact, was obtained in 90% yield. Unfortunately, even when diol 265 was subjected to more forcing conditions, none of the desired triol 266 was obtained.
We next turned our attention toward identifying methods for incorporation of the MOM ether at an earlier stage in the synthesis. Conversion of aldol adduct 268 to MOM ether 269 proceeded smoothly in 83% yield, a pleasing result since the MOM ether is seldom used in conjunction with the thiazolidinethione auxiliary (Scheme 4.17). Upon elongation of the carbon backbone via cross metathesis with ethyl acrylate, MOM ether 270 was treated with di-iso-butylaluminum hydride to effect reduction of the ester and cleavage of the thiazolidinethione auxiliary. To our surprise, none of desired allylic alcohol 271 was obtained from the reaction mixture. Instead, alcohol 272, formed upon elimination of the MOM ether, was obtained in 44% yield.

This unexpected result prompted us to explore an alternative approach towards MOM-protected tetrahydropyran 267, in which the cross metathesis would be postponed until after cleavage of the auxiliary to prevent elimination. As a result of reordering these steps, the cross metathesis would need to be performed with diacetate 274 to allow for differentiation between C21 and C27 (Scheme 4.18). Toward this end, MOM-protected
aldol adduct 269 was treated with di-iso-butylaluminum hydride to effect reductive removal of the thiazolidinethione auxiliary, giving rise to aldehyde 273 in 76% yield. The cross metathesis between aldehyde 273 and diacetate 274 proceeded as planned to give rise to aldehyde 275 in 71% yield. The use of diacetate 274 as the cross metathesis partner also eliminates a step from the synthesis of the tetrahydropyran fragment. Aldehyde 275 could be advanced to MOM-protected tetrahydropyran 267 via the allylation, epoxidation, TES protection sequence, albeit in only 25% yield for the three steps. Tetrahydropyran 267 was prepared in seven steps and 10% overall yield from 3-butenal; on the other hand, TBS-protected tetrahydropyran 228 was available in 32% overall yield by the previously discussed eight step sequence. Based on the significantly lower overall yield with MOM-protected tetrahydropyran 267, we decided to proceed with originally prepared tetrahydropyran 228 with the intention of swapping the C25 TBS ether for a MOM ether upon completion of the bicyclic ether/THP fragment.

**Scheme 4.18.** Synthesis of MOM-protected tetrahydropyran 267.

While we did not end up using tetrahydropyran 267 in our efforts towards sorangicin A, the preparation of this intermediate resulted in the development of a more convenient seven step synthesis of the tetrahydropyran fragment. The reduction, cross metathesis sequence could also be applied toward the synthesis of TBS-protected
tetrahydropyran 228 (Scheme 4.19). From protected aldol adduct 240, reductive removal of the chiral auxiliary delivered aldehyde 278 in 83% yield. Subsequent cross metathesis with diacetate 274 furnished aldehyde 242 in 71% yield. Aldehyde 242 can be carried through the remaining three steps to arrive at tetrahydropyran 228 in seven steps and 31% overall yield, essentially the same as the eight step route involving the cross metathesis with ethyl acrylate.

**Scheme 4.19. Revised approach to tetrahydropyran 228.**

**ii. Optimization of the cross metathesis to form the C29-C30 bond**

Upon realization that we would need to replace the C25 TBS ether at a later stage in the synthesis, we turned our attention toward optimization of the cross metathesis to form the C29-C30 bond. Several conditions were explored for the cross metathesis reaction between PMB-protected bicyclic ether 264 and previously prepared tetrahydropyran 256 (Scheme 4.20). The initial conditions developed by Haley involved syringe pump addition of tetrahydropyran 256 to a solution of the bicyclic ether and Grubbs 2nd generation catalyst. With Piv-protected bicyclic ether 255, the desired product was obtained in 40% yield, with 55% recovered bicyclic ether 255. These results could be replicated with PMB-protected bicyclic ether 264 when the reaction was
run with a 1:1 ratio of tetrahydropyran 256 and bicyclic ether 264 in the presence of 20 mol % Hoveyda-Grubbs 2nd generation catalyst (HG2) in toluene at 60 °C. We were encouraged to find that using an excess of bicyclic ether 264 (2.0 equiv) under otherwise identical conditions increased the yield to 47%. Unfortunately, separation of cross metathesis adduct 279 from bicyclic ether 264 was problematic. In all of the cross metathesis attempts between bicyclic ether 264 and tetrahydropyran 256 we noticed the formation of a byproduct which closely resembled bicyclic ether 264 by NMR. Even when the cross metathesis reactions were conducted at room temperature, a considerable amount of this undesired product was formed. Upon isolation and further evaluation of the NMR, we able to assign the structure as alkyne 280, formed as a result of a cross metathesis reaction between bicyclic ether 264 and the internal C19-C20 olefin of tetrahydropyran 256. As the internal olefin participating in this unwanted cross metathesis reaction is present in both the tetrahydropyran starting material and desired cross metathesis adduct 279, there was no way to suppress the formation of alkyne 280.

Scheme 4.20. Cross metathesis approach to bicyclic ether/THP fragment 279.

As a result of the isolation of byproduct 280, we decided to pursue an alternative route towards bicyclic ether/THP fragment 279. Instead of introducing the C16-C20 fragment prior to the cross metathesis reaction, we would perform the cross metathesis
between bicyclic ether 264 and tetrahydropyran 228 before the vinyl addition of iodide 259 (Scheme 4.21). Interestingly, the cross metathesis reaction between bicyclic ether 264 and tetrahydropyran 228 was far more efficient than the cross metathesis with tetrahydropyran 256, even when run under nearly identical conditions. As before, the tetrahydropyran was added dropwise via syringe pump over several hours to a solution of bicyclic ether 264 and Grubbs 2\textsuperscript{nd} generation catalyst in toluene. The metathesis catalyst was added in three portions over the same period of time to ensure that active catalyst was present in the reaction mixture. To our delight, these conditions provided a 77\% yield of cross metathesis adduct 281. Another advantage of this cross metathesis reaction, as compared to those discussed previously, is the ease with which cross metathesis adduct 281 was separated from excess bicyclic ether 264. With bicyclic ether/THP fragment 281 in hand, installation of the C16-C20 alkyne was explored. Bis-TES ether 281 was converted to aldehyde 282 under the modified Swern conditions in 78\% yield.\textsuperscript{149} Unfortunately, the addition of aldehyde 282 to the transmetallated species derived from vinyl iodide 259 did not effect the desired bond forming event. The recovery of 87\% of the unreacted aldehyde provided evidence that the lack of reactivity was not a result of aldehyde decomposition. Despite several attempts to arrive at C16-C37 fragment 283 by this approach, none of the desired product was ever obtained.
In order to determine if aldehyde 282 was a competent electrophile, an alternative vinyl iodide was prepared and employed in the addition reaction. Vinyl iodide 285 was chosen as a suitable C16-C20 surrogate as the terminal olefin, necessary for the second cross metathesis reaction, could be readily accessed from the C16 primary alcohol. In addition, having an alcohol at this position instead of an alkyne offers the flexibility to explore alternative coupling strategies for introducing the dihydropyran moiety. Thus, vinyl iodide 285, available from 4-pentynol in two steps via a TBS protection, hydrozirconation/iodination sequence, was prepared in 76% yield (Scheme 4.22). To our delight, upon in situ generation of the vinylzinc species from iodide 285 followed by addition of aldehyde 282, vinyl addition product 286 was obtained in 78% yield with only one diastereomer detectable by NMR.
4.5 C1-C20 Vinyl iodide approach towards assembly of the natural product

With a viable route towards C16-C37 fragment 286, attention could be turned to introduction of the dihydropyran fragment. However, based on the success of the vinyl addition with iodide 285, we first wanted to investigate whether the entire dihydropyran fragment could be installed in a similar fashion. In our revised retrosynthetic analysis, we envisioned preparing C1-C37 fragment 287 by the addition of C1-C20 vinyl iodide 288 into aldehyde 282, available by the previously discussed cross metathesis between tetrahydropyran 228 and bicyclic ether 264 (Scheme 4.23).
In order to explore this revised synthetic approach, the preparation of C1-C20 vinyl iodide 288 was necessary. Elongation of the carbon backbone of alcohol 251, an intermediate from the synthesis of dihydropyran 229, was accomplished by a cross metathesis with diyne 289 in an unoptimized 62% yield (Scheme 4.24). Deprotection of the TIPS alkyne was achieved upon exposure of cross metathesis adduct 290 to TBAF. The primary alcohol was protected as the TBS ether under standard conditions, furnishing alkyne 291 in 76% yield over the two steps. Finally, a hydrozirconation/iodination sequence generated vinyl iodide 288 in 72% yield.\[^{156}\]
The addition reaction of vinyl iodide 288 to aldehyde 282 was run under the previously optimized conditions (Scheme 4.25). Disappointingly, only unreacted aldehyde 282 and terminal olefin 292, formed upon quenching of the in situ generated vinylzinc species, were obtained from the reaction. Isolation of terminal olefin 292 in 60% yield provided evidence that the vinyl iodide was undergoing transmetallation, but not addition into the aldehyde. Several unsuccessful attempts to effect the desired transformation prompted us to explore an alternative coupling strategy.
4.6  Julia olefination approach towards assembly of the natural product

At this point we shifted our focus to the advancement of bicyclic ether/THP fragment 286 towards the completion of the natural product. An advantage of this C16-C37 fragment over the previously prepared intermediate bearing a terminal olefin at C16 is the opportunity to easily explore other coupling reactions as a result of the added flexibility of the C16 alcohol. While the cross metathesis approach toward appendage of the dihydropyran fragment had provided some promising results, upon careful consideration of this coupling strategy several concerns arose. Most notably, the selectivity of the cross metathesis reaction which features two Type I olefins in dihydropyran 229 and the olefin derived from bicyclic ether/THP fragment 286. In addition, the number of steps necessary to prepare the terminal olefin from C16-C37 fragment 286 would require an extra step when compared to olefination strategies which feature an aldehyde coupling partner. For these reasons, we decided to pursue a Julia...
olefination to unite the dihydropyran unit with the rest of the molecule. An analogous strategy was successfully employed by Smith and co-workers in the only total synthesis of (+)-sorangicin A to date. For the Julia olefination strategy, we sought to prepare the same C16-C38 aldehyde 173 and C1-C15 sulfone 132 coupling partners as those prepared by Smith (Scheme 4.26). Aldehyde 173 would be accessed from bicyclic ether/THP fragment 286, which was prepared in an efficient manner by a cross metathesis between bicyclic ether 264 and tetrahydropyran 228. The synthesis of sulfone 132 would require significant modification of our synthesis of dihydropyran 229 in order to accommodate the sulfone at C15 as opposed to a terminal olefin.

i. **Synthesis of C1-C15 sulfone 132**

In order to access sulfone 132 in an efficient manner, modification of the original approach towards dihydropyran 229 was necessary, as we now required a sulfone at C15 instead of a terminal olefin. Upon evaluation of the route developed by Haley for accessing dihydropyran 229, we determined that employing TBS-vinyl ether instead of allyltrimethyl silane would facilitate preparation of the requisite sulfone in an efficient manner. Thus, mixed acetal 249 (See Scheme 4.7) would serve as a common intermediate between dihydropyran 229 and sulfone 132. With mixed acetal 249 in hand, Lewis acid mediated addition of TBS-vinyl ether\textsuperscript{157} was explored (Scheme 4.27). Gratifyingly, in the presence of lithium perchlorate, TBS-vinyl ether underwent facile addition into the oxocarbenium ion generated \textit{in situ} from mixed acetal 249, affording aldehyde 293 in 82% yield as a single diastereomer.\textsuperscript{158} Subsequent sodium borohydride reduction delivered alcohol 294 in 97% yield. In order to intercept the sulfone intermediate prepared in Smith’s total synthesis, replacement of the methoxymethyl (MOM) ether with a TBS ether was necessary. The MOM ether was effectively cleaved with 15% hydrochloric acid in tert-butanol to deliver an intermediate diol, which was converted to bis-TBS dihydropyran 295 in 80% yield over the two step sequence. Introduction of the desired oxidation state at C1 was achieved by the four step sequence developed by Smith.\textsuperscript{84} Removal of the \textit{p}-methoxybenzyl (PMB) ether with DDQ, followed by Dess-Martin oxidation gave rise to aldehyde 296 in 77% yield over the two steps. Further oxidation to the acid was achieved under Pinnick conditions; the crude acid was subsequently exposed to \textit{tert}-butyl isourea 159 to afford \textit{tert}-butyl ester 162 in 83% yield.
Ester 162 is a common intermediate from Smith's synthesis of the dihydropyran fragment. Thus, the same three step sequence employed by Smith could be utilized to convert tert-butyl ester 162 to sulfone 132, beginning with selective removal of the primary TBS ether (Scheme 4.28). The treatment of ester 162 with TBAF at 0 °C effected cleavage of the primary TBS ether, in the presence of the secondary TBS ether, to deliver alcohol 297 in 76% yield. The resultant primary alcohol underwent a Mitsunobu reaction\textsuperscript{100} with 1-phenyltetrazole-5-thiol to give rise to an intermediate thioether, which was oxidized under standard conditions to sulfone 162 in 68% yield over the two steps. This route enables the preparation of C1-C15 sulfone 162 in 17 steps and 11.4% overall yield from known aldehyde 154.
ii. Completion of Smith’s C1-C38 fragment of (+)-sorangicin A

Having developed an efficient route towards sulfone 132, the preparation of the aldehyde coupling partner was the next task at hand. In order to prepare aldehyde 173 from bicyclic ether/THP fragment 286, several protecting group manipulations were necessary. It was envisioned that the most efficient manner for arriving at the desired C16-C37 substrate was to remove all of the silyl protecting groups from bicyclic ether/THP fragment 286 and systematically reprotect the resultant tetraol. To our delight, tetraol 299 was readily obtained in 75% yield upon treatment of the previously discussed vinyl addition product 286 with several equivalents of TBAF (Scheme 4.29). The protection strategy devised for tetraol 299 involved initial formation of the C21-C22 acetonide, followed by selective protection of the primary alcohol as the TBS ether, and finally formation of the C25 MOM ether. Toward this end, tetraol 299 was exposed to a catalytic amount of camphorsulfonic acid (CSA) in neat 2, 2-dimethoxypropane. These conditions not only form the C21-C22 acetonide, but also protect the primary alcohol as the 2-methoxy-2-propyl (MOP) ether. Acidic workup effectively cleaved the MOP ether
to deliver acetonide 300 in 95% yield. Selective protection of the primary alcohol as the TBS ether in the presence of the C25 secondary alcohol was readily accomplished with tert-butyldimethylsilyl chloride and imidazole as the base. Even in the presence of excess silylating reagent, the primary TBS ether was obtained exclusively in 78% yield. The remaining unprotected alcohol at C25 was converted to the MOM ether with methoxymethyl iodide, generated in situ from methoxymethyl chloride and sodium iodide, affording fully protected C16-C37 fragment 301 in 95% yield.

Introduction of the C37-C38 vinyl iodide by a Takai olefination was pursued.

Oxidative removal of the p-methoxybenzyl (PMB) ether was effected upon treatment of p-methoxybenzyl ether 301 with DDQ to give rise to alcohol 302 in 83% yield (Scheme 4.30). Subsequent Dess-Martin oxidation proceeded smoothly to deliver aldehyde 303 in 95% yield. The aldehyde was exposed to chromium chloride and iodoform in a 4:1 mixture of dioxane and THF to effect the Takai olefination. The requisite vinyl iodide was obtained as a 4:1 of mixture of E/Z olefin isomers, which were readily separated by

Scheme 4.29. Synthesis of fully protected C16-C37 fragment 301.
flash column chromatography to afford \( E \)-vinyl iodide 172 in 40% yield and \( Z \)-vinyl iodide 304 in 11% yield.

\[ \text{Scheme 4.30. Synthesis of C16-C38 vinyl iodide 172.} \]

Vinyl iodide 172 is a common intermediate from Smith's total synthesis of (+)-sorangicin A, serving as a precursor to aldehyde 173. With an efficient route towards vinyl iodide 172 in hand, we carried out the three step sequence described by Smith to arrive at the coupled C1-C38 fragment (Scheme 4.31). To arrive at the aldehyde required for the Julia olefination, the TBS ether was cleaved and subjected to Dess-Martin oxidation. Finally, with both coupling partners in hand, the Julia olefination between aldehyde 173 and sulfone 132 to form the C15-C16 bond was achieved to deliver C1-C38 fragment 174 in 79% yield.
4.7 Summary

In summary, a formal synthesis of the C1-C38 fragment prepared by Smith en route to the total synthesis of (+)-sorangicin A was completed in 25 steps over the longest linear sequence. The three key fragments: bicyclic ether 264, tetrahydropyran 228, and dihydropyran 132 were prepared in 12, 7, and 19 steps respectively. Cross metathesis proved to be an efficient strategy for coupling the bicyclic ether and tetrahydropyran fragments. The identification of a consistent and high-yielding approach for uniting the C1-C15 dihydropyran fragment to the rest of the molecule proved to be a considerable challenge. Our modular approach towards sorangicin A allowed us to explore several coupling strategies; ultimately, a Julia olefination to form the C15-C16 bond, also employed in Smith’s total synthesis, resulted in the formal synthesis of the C1-C38 fragment of (+)-sorangicin A.
CHAPTER FIVE

Experimental and NMR Spectra: Spirofungins A and B

5.1 Materials and Methods

Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer and values reported in cm$^{-1}$. Proton and carbon nuclear magnetic resonance spectra (NMR) were acquired on a Bruker model Avance 400 ($^1$H at 400 MHz; $^{13}$C at 100 MHz, CDCl$_3$) or Bruker model Avance 500 ($^1$H at 500 MHz; 13C at 125 MHz, CDCl$_3$). Chemical shifts are reported relative to chloroform, $\delta$ 7.26 for $^1$H NMR spectra and $\delta$ 77.2 for $^{13}$C NMR spectra. Optical rotations were determined using a Jasco P1010 polarimeter. Mass spectra were obtained using a Bruker BioTOF II mass spectrometer with electrospray ionization (ESI). Thin layer chromatography (TLC) was conducted on silica gel F254 TLC plates purchased from Scientific Adsorbents, Inc. Flash column chromatography was carried out using Ultra Pure Silica Gel Silia-P (40 to 63 $\mu$m) purchased from SiliCycle Inc. The second generation Grubbs precatalyst (G2) is defined as [Ru=CHPh(Cl)$_2$(PCy$_3$)(DHIMes)]. Diethyl ether (Et$_2$O), tetrahydrofuran (THF), dichloromethane (CH$_2$Cl$_2$), and toluene were dried by being passed through a column of neutral alumina under nitrogen immediately prior to use. Alkylamines were distilled from calcium hydride immediately prior to use. All other reagents and solvents were used as
received from the manufacturer, unless otherwise specified. All air and water sensitive reactions were performed in flasks flame dried under positive flow argon and conducted under an argon atmosphere.

5.2 Experimental Procedures

**Aldol adduct 57:** To a dry round bottom flask under argon was added N-acetylthiazolidinethione 56 (5.01 g, 17.93 mmol) in 85 mL CH$_2$Cl$_2$. The solution was cooled to $-78^\circ$C and titanium tetrachloride (1.92 mL, 17.93 mmol) was added dropwise. The thick suspension was stirred 10 minutes, upon which diisopropylethylamine (3.13 mL, 17.93 mmol) was added dropwise. The solution was stirred at $-78^\circ$C for 45 minutes at which time freshly prepared 3-butenal (in CH$_2$Cl$_2$, 1.14 g, 16.31 mmol) was added dropwise. The reaction was stirred at $-78^\circ$C for 1 h then quenched with half saturated ammonium chloride and warmed to room temperature. The layers were separated and the aqueous layer extracted twice with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10-15% EtOAc/Hex) to provide the product (4.6 g, 81%) as a yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 2.14-2.29 (m, 2H), 2.25 (s, 3H), 2.39 (br. s., 6H), 2.85 (d, $J=4.1$ Hz, 1H), 3.19 (dd, $J=17.4$, 2.8 Hz, 1H), 3.33 (dd, $J=11.2$, 9.6 Hz, 1H), 3.51-3.60 (m, 2H) 3.95 (m, 1 H) 5.09 (m, 2H) 5.76 (dddd, $J=16.7$, 14.0, 9.4, 7.3 Hz, 1H), 6.37 (t, $J=9.8$ Hz, 1H), 6.85 (br. s., 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 20.5, 21.0, 32.7, 41.0, 46.1, 67.9, 68.2, 118.3, 132.8, 134.1, 138.1, 174.8, 201.9; IR (film): 3447 (br), 3074, 3006, 2971, 2921, 2868, 2734, 1705, 1610,
1371, 1260, 1177, 1049, 912, 731; ESI-MS: C_{18}H_{23}NO_{2}S_{2} \ [M+Na] \text{ calc.} 372.1, \text{ found } 372.1; [\alpha]_{D}^{24} = -112.1^\circ (c = 0.95, \text{CH}_2\text{Cl}_2).

Iso-butyl ester 59: To a dry round bottom flask were added aldol adduct 57 (1.85 g, 5.29 mmol), imidazole (0.72 g, 10.58 mmol), iso-butyl alcohol (4.8 mL, 52.88 mmol) and 10 mL CH\_2Cl\_2. The reaction mixture was stirred for 12 hours at room temperature, then diluted with CH\_2Cl\_2 and quenched with water. The aqueous layer was extracted twice with CH\_2Cl\_2. The combined organic layers were dried over Na\_2SO\_4, filtered, and concentrated under reduced pressure. To remove the free auxiliary, the crude product was taken up in hexanes and the minimum amount of ethyl acetate and washed twice with 1 M NaOH. The organic layer was dried over Na\_2SO\_4, filtered, and concentrated under reduced pressure. The crude ester was purified by flash column chromatography (3\% Et\_2O/CH\_2Cl\_2) to give the product (0.964 g, 98\%) as a light yellow oil. \^H NMR (400 MHz, CDCl\_3) \delta 0.93 (d, J= 6.8 Hz, 6H), 1.94 (q, J= 6.6 Hz, 1H), 2.22-2.35 (m, 2H), 2.44 (dd, J= 16.7, 9.1 Hz, 1H), 2.53 (dd, J= 16.3, 3.0 Hz, 1H), 2.92 (br. s., 1H), 3.90 (d, J= 6.5 Hz, 2H), 4.09 (br. s., 1H), 5.09-5.18 (m, 2H), 5.82 (dq, J= 17.1, 7.2 Hz, 1H); \^C NMR (125 MHz, CDCl\_3): \delta 19.2, 27.8, 40.7, 41.1, 67.5, 71.0, 118.4, 134.1, 173.1; IR (film): 3440, 2964, 2876, 1734, 1381, 1172, 1055, 998, 917 cm\(^{-1}\); ESI-MS: C\textsubscript{10}H\textsubscript{18}O\textsubscript{3} \ [M+Na] \text{ calc.} 209.12, \text{ found } 209.10; [\alpha]_{D}^{25} = -17.6^\circ (c = 0.70, \text{CH}_2\text{Cl}_2).

Alkylated iso-butyl ester 61: To a dry, 3-neck round bottom flask equipped with an internal thermometer was added di-iso-propylamine (1.80 mL, 12.9 mmol) and 12 mL THF. The solution was cooled to –78 °C upon which \textit{n}-butyllithium (1.6M in hexanes, 8.0
mL, 12.9 mmol) was added dropwise. The solution was allowed to come to 0 °C, stirred for 30 minutes, then cooled back to –78 °C. Ester 59 (0.80 g, 4.30 mmol) in 3.3 mL THF was added dropwise. The solution was then warmed slowly to –25 °C over 30 minutes. A solution of methyl iodide (0.67 mL, 10.8 mmol) and 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) (2.0 mL, 16.8 mmol) was added to the reaction mixture. Over the next 30 minutes, the solution was warmed to 0 °C and then stirred for 1 hour. The reaction was quenched with water and extracted three times with diethylether. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (8% EtOAc/Hex) to provide the product (0.54 g, 63%) as a light yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 0.92 (d, J = 6.6 Hz, 6H), 1.20 (d, J = 7.1 Hz, 3H), 1.93 (dddd, J = 13.5, 6.6 Hz, 1H), 2.15-2.25 (m, 1H), 2.28-2.37 (m, 1H), 2.56 (quin, J = 7.0 Hz, 1H), 3.70-3.78 (m, 1H), 3.85-3.91 (m, 2H), 5.08-5.16 (m, 2H), 5.84 (dq, J = 17.0, 7.1 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 14.3, 19.2, 27.8, 39.2, 44.7, 70.8, 72.6, 118.2, 134.4, 176.0; IR (film): 3462, 2965, 2876, 1733, 1468, 1381, 1186, 1042, 993, 915 cm⁻¹; ESI-MS: C₁₁H₂₀O₃ [M+Na] calc. 223.13, found 223.11; [α]²⁵_D = –11.2° (c = 0.08, CH₂Cl₂).

**TES-protected iso-butyl ester 62:** To a dry round bottom flask under argon was added ester 61 (0.52 g, 2.60 mmol) in 22 mL CH₂Cl₂. The solution was cooled to 0 °C and 2,6-lutidine (0.90 mL, 7.8 mmol) was added, followed by dropwise addition of TESOTf (0.90 mL, 3.9 mmol). The reaction was stirred at 0 °C for 1 hour. The reaction was quenched with saturated NaHCO₃ and extracted twice with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (3% EtOAc/Hex) to provide the
product (0.78 g, 96%) as a colorless oil. $^1H$ NMR (400 MHz, CDCl$_3$) $\delta$ 0.59 (q, $J=7.8$ Hz, 6H), 0.89-0.98 (m, 15H), 1.10 (d, $J=6.8$ Hz, 3H), 1.93 (dddd, $J=13.3$, 6.6 Hz, 1H), 2.18-2.32 (m, 2H), 2.63 (quin, $J=6.9$ Hz, 1H), 3.85 (d, $J=6.8$ Hz, 2H), 4.03 (q, $J=5.7$ Hz, 1H), 4.98-5.12 (m, 2H, 5.78-5.92 (m, 1H); $^{13}C$ NMR (100 MHz, CDCl$_3$): $\delta$ 5.2, 7.0, 12.3, 19.3, 27.9, 38.6, 45.9, 70.6, 73.5, 117.4, 134.8, 174.9; IR (film): 2958, 2913, 2877, 1738, 1461, 1380, 1175, 1087, 1004, 912 cm$^{-1}$; ESI-MS: C$_{17}$H$_{34}$O$_3$Si [M+Na] calc. 337.22, found 337.19; $[^{25}\alpha]D = -30.8^\circ$ (c = 1.03, CH$_2$Cl$_2$).

**Aldehyde 55:** To a dry mL round bottom flask under argon was added TES-protected ester 62 (0.64 g, 2.05 mmol) in 17 mL CH$_2$Cl$_2$. The solution was cooled to −78 °C and DIBAL (1M in hexanes, 2.1 mL, 2.1 mmol) was added dropwise via syringe. The reaction was stirred 20 minutes and then quenched with saturated potassium sodium tartrate. Upon warming to room temperature, the quenched reaction was vigorously stirred for 2 hours. The layers were separated and the aqueous layer extracted twice with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (4% EtOAc/Hex) to provide the product (0.46g, 93%) as a colorless oil. $^1H$ NMR (400 MHz, CDCl$_3$) $\delta$ 0.63 (q, $J=7.8$ Hz, 6H), 0.98 (t, $J=8.0$ Hz, 9 H), 1.10 (d, $J=6.8$ Hz, 3H), 2.25-2.43 (m, 2H), 2.49-2.60 (m, 1H), 4.00 (q, $J=5.3$ Hz, 1H), 5.02-5.19 (m, 2H, 5.76-5.91 (m, 1H), 9.79 (s, 1H); $^{13}C$ NMR (100 MHz, CDCl$_3$): $\delta$ 5.2, 7.0, 10.7, 40.0, 51.0, 73.5, 118.3, 133.9, 205.1; IR (film): 2956, 2913, 2877, 1725, 1459, 1239, 1005, 914 cm$^{-1}$; ESI-MS: C$_{13}$H$_{26}$O$_2$Si [M+Na] calc. 265.16, found 265.14; $[^{25}\alpha]D = -37.5^\circ$ (c = 0.88, CH$_2$Cl$_2$).
Aldol adduct 64: To a dry round bottom flask under argon was added thiazolidinethione 63 (2.65 g, 10.0 mmol) in 60 mL CH₂Cl₂. The solution was cooled to 0 °C and titanium tetrachloride (1.15 mL, 10.5 mmol) was added dropwise. The thick suspension was stirred five minutes, upon which (−)-sparteine (2.3 mL, 10.0 mmol) was added dropwise. After 10 minutes stirring, the solution was cooled to −78 °C and N-methyl pyrrolidinone (0.96 mL, 10.0 mmol) was added. After stirring for 20 minutes, acrolein (neat, 0.74 mL, 11.0 mmol) was added dropwise. The reaction was stirred for 1 hour at −78 °C then warmed slowly to 0 °C for 1 hour. The reaction was quenched with half saturated ammonium chloride and warmed to room temperature. The layers were separated and the aqueous layer extracted twice with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (25% EtOAc/Hex) to provide the product (3.10 g, 96%) as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ ppm 1.22 (d, J= 6.6 Hz, 3H, 2.59 (br. s., 1 H), 2.87 (d, J= 11.5 Hz, 1 H), 3.02 (dd, J= 11.0, 12.6 Hz, 1 H), 3.20 (dd, J= 13.1, 3.4 Hz, 1 H), 3.36 (dd, J= 11.5, 7.1 Hz, 1 H), 4.45 (br. s., 1 H), 4.53 (ddd, J= 13.5, 10.8, 6.6 Hz, 1 H), 5.18 (d, J= 10.5 Hz, 1 H), 5.24-5.33 (m, 2H, 5.80 (ddd, J= 16.90, 10.83, 5.50 Hz, 1 H), 7.21-7.34 (m, 5 H); ¹³C NMR (125 MHz, CDCl₃): δ 11.2, 32.4, 36.9, 43.9, 69.1, 73.7, 116.5, 127.5, 129.1, 129.6, 136.5, 137.7, 177.6, 201.6; IR (film): 3443, 3062, 3027, 2981, 2936, 2876, 1695, 1454, 1342, 1262, 1192, 1167, 1137 cm⁻¹; ESI-MS: C₁₆H₁₉NO₂S₂ [M+Na] calc. 344.08, found 344.07; [α]₂⁵°₀ = −152.4° (c = 1.95, CH₂Cl₂).
**Protected aldol adduct:** To a dry round bottom flask under argon was added aldol adduct 64 (1.40 g, 4.4 mmol) in 45 mL CH$_2$Cl$_2$. The solution was cooled to 0 °C and 2,6-lutidine (1.5 mL, 13.2 mmol) was added, followed by dropwise addition of TESOTf (1.5 mL, 6.6 mmol). The reaction was stirred at 0 °C for 1 hour. The reaction was quenched with saturated NaHCO$_3$ and extracted twice with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5% EtOAc/Hex) to provide the product (1.76 g, 92%) as a yellow oil. ^1^H NMR (500 MHz, CDCl$_3$) δ ppm 0.61 (q, J= 7.9, 6 H), 0.96 (t, J= 7.9 Hz, 9 H), 1.27 (d, J= 6.6 Hz, 3H), 2.91 (d, J= 11.5 Hz, 1 H), 3.07 (dd, J= 12.9, 11.1 Hz, 1 H), 3.28-3.36 (m, 2H), 4.33 (t, J= 6.8 Hz, 1 H), 4.62 (quin, J= 6.6 Hz, 1 H), 5.05-5.16 (m, 2H), 5.20 (d, J= 17.2 Hz, 1 H), 5.89 (dd, J= 17.2, 10.1, 7.2 Hz, 1 H), 7.27-7.40 (m, 5 H); ^13^C NMR (125 MHz, CDCl$_3$): δ 5.0, 7.0, 13.0, 32.6, 36.6, 46.0, 69.7, 76.8, 116.0, 127.3, 129.0, 129.6, 136.8, 139.2, 176.6, 201.3; IR (film): 2921, 1691, 1364, 1341, 1263, 1165, 1138, 1044 cm$^{-1}$; ESI-MS: C$_{22}$H$_{33}$NO$_2$S$_2$Si [M+Na] calc.458.16, found 458.13; [α]$^D_{25}$ = −152.3° (c = 1.80, CH$_2$Cl$_2$).

**Aldehyde 65:** To a dry mL round bottom flask under argon was added the protected aldol adduct (1.30 g, 3.0 mmol) in 30 mL CH$_2$Cl$_2$. The yellow solution was cooled to −78 °C and DIBAL (1M in hexanes) was added dropwise via syringe until the reaction mixture became colorless (4.5 mL, 4.5 mmol). The reaction mixture was immediately quenched with saturated potassium sodium tartrate, warmed to room temperature, and
vigorously stirred for 2 hours. The layers were separated and the aqueous layer extracted twice with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (4% EtOAc/Hex) to provide the product (0.685 g, 100%) as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ ppm 0.58 (q, J= 8.0 Hz, 6 H), 0.93 (t, J= 8.0 Hz, 9 H), 1.06 (d, J= 6.8 Hz, 3H), 2.43 - 2.52 (m, 1 H), 4.51 (t, J= 5.3 Hz, 1H), 5.17 (d, J= 10.5 Hz, 1 H), 5.25 (d, J= 17.0 Hz, 1 H), 5.83 (ddd, J= 17.0, 10.5, 6.5 Hz, 1 H), 9.77 (s, 1 H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 5.0, 7.0, 8.6, 52.7, 73.9, 116.2, 138.4, 205.0; IR (film): 2956, 2912, 2878, 1726, 1459, 1415, 1240, 1081, 1034, 1017 cm$^{-1}$; ESI-MS: C$_{12}$H$_{24}$O$_2$Si [M+Na] calc. 251.14, found 251.13; [$\alpha$]$^24$ D = −51.8° (c = 1.43, CH$_2$Cl$_2$).

**α, β-unsaturated ester 70**: To a dry round bottom flask equipped with a condenser was added aldehyde 65 (0.684 g, 3.0 mmol), ylide 69 (1.57 g, 4.5 mmol), and 30 mL THF. The reaction was stirred at reflux for 12 hours then cooled to room temperature and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5% EA/Hex) to provide the product (0.805 g, 91%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 0.58 (q, J= 7.7 Hz, 6H), 0.94 (t, J= 8.0 Hz, 9H), 1.03 (d, J= 6.8 Hz, 3H), 1.28 (t, J= 7.2 Hz, 3H) 2.38 - 2.49 (m, 1 H) 4.03 (t, J= 5.9 Hz, 1 H) 4.18 (q, J= 7.2 Hz, 2H) 5.10 (d, J= 10.2 Hz, 1H), 5.15 (d, J= 17.2 Hz, 1H) 5.75 (ddd, J= 17.2, 10.2, 6.5 Hz, 1H), 5.78 (d, J= 15.9 Hz, 1H), 6.98 (dd, J= 15.8, 7.4 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 5.1, 6.6, 7.0, 14.4, 43.3, 60.3, 77.0, 115.9, 121.3, 139.1, 151.3, 166.9; IR (film): 2957, 2911, 2877, 1722, 1654, 1459, 1367, 1269, 1181, 1035 cm$^{-1}$; ESI-MS: C$_{16}$H$_{30}$O$_3$Si [M+Na] calc. 321.19, found 321.16; [$\alpha$]$^{25}$ D = −21.5° (c = 1.18, CH$_2$Cl$_2$).
Allylic alcohol 49: To a dry round bottom flask under argon was added $\alpha,\beta$-unsaturated ester 70 (0.35 g, 1.17 mmol) and 11.7 mL THF. The solution was cooled to 0 °C upon which TBAF (1 M in THF) was added dropwise (2.35 mL, 2.35 mmol). After 30 minutes, the reaction was quenched with saturated NaHCO$_3$ then extracted twice with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10-20% EtOAc/Hex) to provide the product (0.205 g, 95%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.09 (d, $J$= 6.8 Hz, 3H) 1.29 (t, $J$= 7.2 Hz, 3H) 1.59 (br. s., 1H) 2.48 - 2.59 (m, 1H) 4.11 (m, 1H) 4.19 (q, $J$= 7.2 Hz, 2H) 5.21 (d, $J$= 10.3 Hz, 1H) 5.27 (d, $J$= 17.2 Hz, 1H) 5.84 (ddd, $J$= 17.2, 10.3, 6.1 Hz, 1H) 5.87 (d, $J$= 16.3 Hz, 1H) 6.96 (dd, $J$= 15.6, 7.6 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 14.37, 14.39, 42.3, 60.5, 75.9, 116.7, 122.1, 138.3, 150.2, 166.7; IR (film): 3434, 2980, 1718, 1652, 1370, 1276, 1183, 1035 cm$^{-1}$; ESI-MS: C$_{10}$H$_{16}$O$_3$ [2M+Na] calc. 391.21, found 391.22; $[^{13}\alpha]_D^{24} = -0.36^\circ$ (c = 12.4, CH$_2$Cl$_2$).

Dienoate 108: To a dry round bottom flask equipped with a condenser was added aldehyde 107 (1.80 g, 8.39 mmol), ylide 69 (3.89 g, 10.91 mmol), and 42 mL THF. The reaction was stirred at reflux for 12 hours then cooled to room temperature and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5% EA/Hex) to provide the product (2.10 g, 88%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.07 (s, 6H), 0.90 (s, 9H), 1.30 (t, $J$= 7.0 Hz, 3H), 1.76 (s, 3H),
4.21 (q, J = 7.2 Hz, 2H), 4.36 (d, J = 5.7 Hz, 2H), 5.84 (d, J = 15.9 Hz, 1H), 5.95 (t, J = 5.9, 1H) 7.30 (d, J = 15.9 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ -5.0, 12.6, 14.5, 18.5, 26.1, 60.4, 60.5, 117.3, 132.7, 140.4, 148.7, 167.4.

**Aldehyde 109:** To a dry round bottom flask equipped with an addition funnel was added dienoate 108 (2.10 g, 7.37 mmol) and 74 mL CH$_2$Cl$_2$. The solution was cooled to −78 °C and DIBAL (1M in hexanes, 18.4 mL, 18.4 mmol) was added dropwise via addition funnel. After 30 minutes stirring, the reaction was quenched with saturated potassium sodium tartrate, warmed to room temperature, and vigorously stirred for 2 hours. The layers were separated and the aqueous layer extracted twice with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude alcohol was used in the next reaction without further purification. $^1$H NMR (500 MHz, CDCl$_3$) δ 0.06 (s, 6H), 0.89 (s, 9H), 1.74 (s, 3H), 4.20 (d, J = 5.7 Hz, 2H), 4.31 (d, J = 6.2 Hz, 2H), 5.58 (t, J = 6.1 Hz, 1H) 5.78 (dt, J = 15.7, 6.0 Hz, 1H), 6.25 (d, J = 15.6 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ -5.0, 12.8, 18.5, 26.1, 60.4, 63.9, 127.1, 132.2, 133.5, 135.9.

To a dry round bottom flask was added the alcohol (1.79 g, 7.37 mmol) and 49 mL CH$_2$Cl$_2$. Manganese dioxide (7.69 g, 88.4 mmol) was added and the reaction stirred at room temperature for 12 hrs. The reaction was filtered over Celite, washing with CH$_2$Cl$_2$ then concentrated under reduced pressure. Aldehyde 109 was used immediately in the next reaction without further purification. $^1$H NMR (400 MHz, CDCl$_3$) δ 0.09 (s, 6H), 0.91 (s, 9H), 1.81 (s, 3H), 4.40 (d, J = 5.7 Hz, 2H), 6.08 (t, J = 5.7 Hz, 1H), 6.14 (dd, J = 15.8, 7.8 Hz, 1H), 7.11 (d, J = 15.6 Hz, 1H), 9.58 (d, J = 8.0 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ -5.0, 12.8, 18.5, 26.0, 60.7, 128.0, 132.9, 143.0, 157.0, 194.4.
Aldol adduct 110: To a dry round bottom flask under argon was added thiazolidinethione 63 (1.76 g, 6.65 mmol) in 50 mL CH$_2$Cl$_2$. The solution was cooled to 0 °C and titanium tetrachloride (0.74 mL, 7.0 mmol) was added dropwise. The thick suspension was stirred five minutes, upon which (−)-sparteine (1.5 mL, 6.65 mmol) was added dropwise. The dark red solution was stirred for 20 min at 0 °C, then cooled to −78 °C and N-methyl pyrrolidinone (0.64 mL, 6.65 mmol) was added. The mixture was stirred 10 min at −78 °C then aldehyde 109 (in CH$_2$Cl$_2$, 1.75 g, 7.30 mmol) was added dropwise. The reaction was stirred for 1 hour at −78 °C then warmed slowly to 0 °C for 1 hour. The reaction was quenched with half saturated ammonium chloride and warmed to room temperature. The layers were separated and the aqueous layer extracted twice with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10-20% EtOAc/Hex) to provide the product (2.95 g, 88%) as a yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.28 (d, J= 6.5, 3H), 1.73 (s, 3H), 2.45 (br. s., 1H), 2.87 (d, J= 11.5 Hz, 1H), 3.03 (dd, J= 10.5, 13.0 Hz, 1H), 3.23 (dd, J= 3.5, 13.3 Hz, 1H), 3.32 (dd, J= 7.2, 11.4 Hz, 1H), 4.29 (d, J= 6.0 Hz, 2H), 4.48 (t, J= 5.5 Hz, 1H), 4.59 (m, 1H), 5.24 (dd, J= 4.0, 6.5, 10.5 Hz, 1H), 5.59-5.63 (m, 2H), 6.28 (d, J= 16.0 Hz, 1H), 7.27-7.35 (m, 5H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ −5.0, 11.7, 12.9, 18.5, 26.1, 32.4, 36.8, 44.6, 60.3, 69.1, 74.2, 127.4, 127.5, 129.1, 129.6, 132.9, 133.3, 136.1, 136.5, 177.6, 201.5; IR (film): 3414, 2953, 2928, 2856, 1696, 1342, 1260, 1165, 1059, 836 cm$^{-1}$; ESI-MS: C$_{26}$H$_{39}$NO$_3$S$_2$Si [M+Na] calc. 528.20, found 528.16; [α]$^2_D$ = −104.6° (c = 1.31, CH$_2$Cl$_2$).
**TES-protected aldol adduct**: To a dry round bottom flask under argon was added aldol adduct 110 (0.54 g, 1.07 mmol) in 10 mL CH₂Cl₂. Upon cooling the solution to 0 °C, 2,6-lutidine (0.37 mL, 3.20 mmol) was added, followed by dropwise addition of TESOTf (0.36 mL, 1.60 mmol). The reaction was stirred at 0 °C for 1 hour. The reaction was quenched with saturated NaHCO₃ and extracted twice with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5% EtOAc/Hex) to provide the product (0.654 g, 99%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 0.04 (s, 6H), 0.55 (q, J= 8.2 Hz, 6H), 0.85 (s, 9H), 0.92 (t, J= 8.0 Hz, 9H), 1.25 (d, J= 6.5 Hz, 3H), 1.72 (s, 3H), 2.82 (d, J= 11.4 Hz, 1H) 3.01 (dd, J= 12.9, 11.0 Hz, 1H), 3.16 (dd, J=11.4, 6.8 Hz, 1H), 3.26 (dd, J= 13.3, 3.0 Hz, 1H), 4.21-4.32 (m, 3H), 4.61 (t, J= 6.8 Hz, 1 H), 4.99 (m, 1H), 5.54 (t, J= 6.1 Hz, 1H), 5.63 (dd, J= 15.8, 7.8 Hz, 1H), 6.11 (d, J= 15.6 Hz, 1H), 7.21-7.38 (m, 5H); ¹³C NMR (125 MHz, CDCl₃): δ −5.0, 5.1, 7.0, 12.9, 13.3, 18.5, 26.1, 32.5, 36.7, 46.6, 60.3, 69.6, 76.9, 127.3, 129.1, 129.4, 129.6, 132.4, 133.5, 135.3, 136.8, 176.8, 201.3; IR (film): 2954, 2876, 2856, 1696, 1456, 1341, 1259, 1164, 1031, 969, 836 cm⁻¹; ESI-MS: C₃₂H₅₃NO₅S₂Si₂ [M+Na] calc. 642.29, found; [α]²⁴_D = −95.8° (c = 1.35, CH₂Cl₂).

**Aldehyde 111**: To a dry mL round bottom flask under argon was added the protected aldol adduct (3.0 g, 4.88 mmol) in 48 mL CH₂Cl₂. The yellow solution was cooled to −78 °C and DIBAL (1M in hexanes) was added dropwise via syringe until the reaction
mixture became colorless (9.8 mL, 9.8 mmol). The reaction mixture was immediately quenched with saturated potassium sodium tartrate, warmed to room temperature, and vigorously stirred for 2 hours. The layers were separated and the aqueous layer extracted twice with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5% EtOAc/Hex) to provide the product (1.62 g, 81%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.07 (s, 6H), 0.57 (q, $J$ = 7.8 Hz, 6H), 0.88-0.97 (m, 18H), 1.06 (d, $J$ = 6.8 Hz, 3H) 1.71 (s, 3H), 2.45-2.55 (m, 1H), 4.31 (d, $J$ = 6.1 Hz, 2H), 4.55 (dd, $J$ = 6.8, 5.0 Hz, 1H), 5.52-5.63 (m, 2H), 6.20 (d, $J$ = 15.6 Hz, 1H) 9.78 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ −5.0, 5.1, 7.0, 8.9, 12.9, 18.6, 26.1, 53.3, 60.4, 74.0, 128.2, 132.5, 133.3, 135.7, 205.1; IR (film): 2955, 2877, 2857, 1727, 1462, 1254, 1103, 1065, 1007 cm$^{-1}$; ESI-MS: C$_{22}$H$_{44}$O$_3$Si$_2$ [M+Na] calc. 435.27, found 435.27; $[^\alpha]^{24}_{D} = −23.5^\circ$ (c = 1.22, CH$_2$Cl$_2$).

**$\alpha,\beta$-unsaturated ester:** To a dry round bottom flask equipped with a condenser was added aldehyde 111 (1.62 g, 3.93 mmol), ylide 69 (2.05 g, 5.9 mmol), and 39 mL THF. The reaction was stirred at reflux for 12 hours then cooled to room temperature and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5% EA/Hex) to provide the product (1.78, 94%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.07 (s, 6H), 0.56 (q, $J$ = 7.7 Hz, 6H), 0.88-0.96 (m, 18H), 1.02 (d, $J$ = 6.8 Hz, 3H), 1.28 (t, $J$ = 7.2 Hz, 3H), 1.70 (s, 3H), 2.40-2.51 (m, 1H) 4.08 (t, $J$ = 6.3 Hz, 1H), 4.18 (q, $J$ = 7.1 Hz, 2H), 4.31 (d, $J$ = 6.1 Hz, 2H) 5.47-5.58 (m, 2H) 5.78 (d, $J$ = 16.0 Hz, 1H) 6.12 (d, $J$ = 15.6 Hz, 1H) 6.99 (dd, $J$ = 15.6, 7.2 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ −5.0, 5.1, 7.0, 13.0, 14.4, 14.6, 18.6, 26.1, 43.8, 60.3, 60.5, 76.9, 121.3, 116
Ethyl ester: To a dry, 2-neck round bottom flask equipped with an internal thermometer was added copper iodide (0.072 g, 0.38 mmol) and 10 mL THF. The solution was cooled to −50 °C at which time MeLi (1.6 M in Et₂O, 0.24 mL, 0.38 mmol), hexamethylphosphoramide (1.9 mL, 1.90 mmol), and DIBAL (1M in hexanes, 3.8 mL, 3.8 mmol) were added successively while maintaining an internal temperature below −40 °C. The brown solution was stirred 30 minutes at −50 °C upon which the α,β-unsaturated ester (0.92 g, 1.9 mmol) in 3.0 mL THF was added dropwise. The reaction was stirred for 1.5 hours at −50 °C, then diluted with ether and quenched with cold 10% HCl. The layers were separated and the organic layer washed twice with cold 10% HCl, then twice with water. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5% EtOAc/Hex) to provide the product (0.768 g, 83%) as a colorless oil. 

1H NMR (400 MHz, CDCl₃) δ 0.08 (s, 6H), 0.56 (q, J= 8.5 Hz, 6H), 0.85-0.97 (m, 21H), 1.25 (t, J= 7.2 Hz, 3H), 1.29 - 1.41 (m, 1H), 1.54 (m, 1H), 1.72 (s, 3H, 1.76-1.89 (m, 1H), 2.26 (s, 2H), 3.98 (m, J= 5.7 Hz, 1H), 4.11 (q, J= 7.2 Hz, 2H), 4.32 (d, J= 6.1 Hz, 2H), 5.54 (m, 2H), 6.11 (d, J= 15.6 Hz, 1H); 13C NMR (125 MHz, CDCl₃): δ -5.0, 5.1, 7.0, 12.9, 14.4, 15.0, 18.6, 26.1, 27.8, 32.7, 39.8, 60.36, 60.44, 77.7, 129.9, 131.2, 133.8, 134.9, 174.2; IR (film): 2955, 2877, 2858, 1738, 1463, 1255, 1100, 1061, 837 cm⁻¹; ESI-MS: C_{26}H_{52}O_{4}Si₂ [M+Na] calc. 507.33, found 507.32; [α]^{24}_D = +0.9° (c = 0.88, CH₂Cl₂).
**β-ketophosphonate 112**: To a dry, round bottom flask equipped with a jacketed addition funnel was added dimethyl methylphosphonate (0.69 mL, 6.3 mmol) and 12 mL THF. The solution was cooled to −78 °C, at which time n-butyllithium (1.6 M in hexanes, 3.9 mL, 6.4 mmol) was added dropwise via the jacketed addition funnel. After the reaction was stirred for 1 hour at −78 °C, the ethyl ester (0.77 g, 1.58 mmol) in 3.0 mL THF was added dropwise via the jacketed addition funnel. The reaction was stirred for 1 hour at −78 °C then quenched with sat. ammonium chloride and warmed to room temperature. The layers were separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (60% EtOAc/Hex) to provide the product (0.774 g, 87%) as a light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 0.07 (s, 6H), 0.55 (q, J= 8.0 Hz, 6H), 0.85 (d, J= 6.8 Hz, 3H), 0.89-0.96 (m, 18H), 1.22-1.38(m, 1H), 1.47-1.58 (m, 1H), 1.72 (s, 3H), 1.76-1.81 (m, 1H), 2.53-2.72 (m, 2H), 3.00-3.15 (m, 2H), 3.76 (s, 3H), 3.79 (s, 3H), 3.97 (dd, J= 7.2, 5.7 Hz, 1H), 4.31 (d, J= 6.1 Hz, 2H), 5.50-5.60 (m, 2H), 6.11 (d, J= 15.6 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ -5.0, 5.1, 7.0, 12.9, 15.3, 18.6, 26.1, 39.7, 40.8, 41.8, 42.6, 53.2, 60.5, 77.8, 129.7, 131.4, 133.8, 135.0, 202.3; IR (film): 2955, 2877, 2857, 1717, 1462, 1257, 1056, 837 cm⁻¹; ESI-MS: C₂₇H₅₅O₆PSi₂ [M+Na] calc. 585.32, found 585.30; [α]²⁵ºD = 1.8° (c = 1.13, CH₂Cl₂).
**α,β-unsaturated ketone**: To a dry round-bottom flask was added β-ketophosphonate 112 (0.835 g, 1.48 mmol) in 3.6 mL THF. To the solution was added anhydrous barium hydroxide (0.195 g, 1.13 mmol) and the mixture was stirred 30 minutes at room temperature. Aldehyde 55 (0.327 g, 1.35 mmol) was added in 4.0 mL of 40:1 THF: H2O, followed by an additional 3.7 mL of 40:1 THF: H2O. The reaction mixture was stirred 1 h at room temperature and was then diluted with EtOAc, filtered over Celite, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (3% EtOAc/Hex) to provide the product (0.798 g, 87%) as a colorless oil. 

**1H NMR** (500 MHz, CDCl3) δ 0.07 (s, 6H) 0.51-0.63 (m, 12H), 0.85-0.99 (m, 30H), 1.06 (d, J= 6.9 Hz, 3H), 1.29-1.40 (m, 1H), 1.49-1.60 (m, 2H), 1.71 (s, 3H), 1.75-1.85 (m, 2H), 2.10-2.26 (m, 2H), 2.40-2.48 (m, 1H), 2.49-2.65 (m, 2H), 3.67 (m, 1H), 3.97 (t, J= 6.1 Hz, 1H), 4.31 (d, J= 6.2 Hz, 2H) 5.01-5.07 (m, 2H), 5.53 (t, J= 6.1 Hz, 1H), 5.57 (dd, J= 15.7, 7.2 Hz, 1H), 5.70-5.81 (m, 1H), 6.05 (d, J= 16.0 Hz, 1H), 6.11 (d, J= 15.8 Hz, 1H), 6.82 (dd, J= 16.0, 8.3 Hz, 1H); 

**13C NMR** (125 MHz, CDCl3): δ -5.0, 5.2, 5.3, 7.1, 7.2, 13.0, 15.3, 16.1, 18.6, 26.2, 27.3, 38.4, 39.9, 40.1, 42.0, 60.5, 75.4, 77.9, 117.6, 130.1, 130.6, 131.3, 133.8, 134.8, 134.9, 149.0, 201.3; IR (film): 2955, 2877, 1676, 1630, 1462, 1415, 1254, 1101, 1064, 1007, 837 cm⁻¹; ESI-MS: C36H74O4Si3 [M+Na] calc 701.48, found 701.32; [α]D²⁵ = -6.0° (c = 1.09, CH2Cl2).
Ketone 113: To a dry, 2-neck round bottom flask equipped with an internal thermometer was added copper iodide (0.052 g, 0.26 mmol) and 12 mL THF. The solution was cooled to −50 °C at which time MeLi (1.6 M in Et₂O, 0.16 mL, 0.26 mmol), hexamethylphosphoramide (1.32 mL, 7.6 mmol), and DIBAL (1M in hexanes, 3.4 mL, 3.4 mmol) were added successively while maintaining an internal temperature below −40 °C. The brown solution was stirred 30 minutes at −50 °C. The enone (0.896 g, 1.32 mmol) in 1.5 mL THF was added dropwise. The reaction was stirred for 1.5 hours at −50 °C, then diluted with ether and quenched with cold 10% HCl. The layers were separated and the organic layer washed twice with cold 10% HCl, then twice with water. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (3% EtOAc/Hex) to provide the product (0.845 g, 94%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 0.07 (s, 6H), 0.51-0.61 (m, 12H), 0.85 (d, J= 6.6 Hz, 3H), 0.89-0.98 (m, 30 H), 1.23-1.37 (m, 2H), 1.45-1.55 (m, 2H), 1.68-1.79 (m, 5H), 2.13-2.23 (m, 2H), 2.28-2.51 (m, 4H), 3.56 (q, J= 5.3 Hz, 1H), 3.96 (t, J= 6.0 Hz, 1H), 4.31 (d, J= 6.2 Hz, 2H), 4.98-5.08 (m, 2H), 5.49-5.61 (m, 2H), 5.76-5.87 (m, 1H), 6.11 (d, J= 15.8 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ -4.9, 5.2, 5.3, 7.1, 7.2, 12.9, 15.0, 15.3, 18.6, 26.1, 26.2, 26.7, 38.1, 38.2, 40.0, 41.0, 41.1, 60.5, 76.1, 77.9, 116.7, 129.9, 131.3, 133.8, 135.0, 136.0, 211.8; IR (film): 2955, 2877, 1715, 1462, 1415, 1254, 1065, 1007, 837 cm⁻¹; ESI-MS: C₃₈H₇₆O₄Si₃ [M+Na] calc. 703.49, found 703.48; [α]²⁴D = −3.3° (c = 0.78, CH₂Cl₂).
Spiroketal 120 and 121: To a dry round bottom flask was added ketone 113 (0.196 g, 0.29 mmol) and 5.8 mL anhydrous methanol. Pyridinium p-toluenesulfonate (PPTS) (0.014 g, 0.06 mmol) was added and the reaction mixture stirred at room temperature for 3 hours. The solution was concentrated under reduced pressure and the crude product purified by flash column chromatography (10-30% EA/Hex) to give 120 (0.052 g, 56%) and 121 (0.0238 g, 26%) as colorless oils.

120 (15S): ¹H NMR (500 MHz, CDCl₃) δ 0.74 (d, J = 6.8 Hz, 3H), 0.78 (d, J = 6.4 Hz, 3H), 1.22-1.58 (m, 8H), 1.66-1.78 (m, 2H), 1.81 (s, 3H), 1.83-1.91 (m, 1H), 2.19-2.35 (m, 2H), 3.46 (ddd, J = 9.2, 4.6, 4.6 Hz, 1H), 4.12 (dd, J = 8.9, 5.3 Hz, 1H), 4.29 (br. s., 2H), 4.97-5.08 (m, 2H) 5.66 (t, J = 6.6 Hz, 1H), 5.89 (dddd, J = 17.2, 10.0, 8.2, 6.0 Hz, 1H), 6.07 (dd, J = 16.5, 10.3 Hz, 1H), 6.19 (d, J = 15.8 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 13.2, 17.5, 17.6, 24.0, 27.8, 33.5, 33.6, 36.1, 36.4, 37.7, 59.6, 74.0, 79.5, 95.7, 116.4, 128.2, 130.0, 135.2, 136.2, 137.3; IR (film): 3416, 2953, 2929, 2870, 1640, 1457, 1381, 1147, 1015, 985 cm⁻¹; ESI-MS: C₂₀H₃₂O₃ [M+Na] calc. 343.22, found 343.22; [α]²⁴D = −79.6° (c = 1.10, CH₂Cl₂).

Note: 2-D NOESY NMR indicated a strong cross peak between H1 (3.46 ppm)-H2 (6.07 ppm) and H1 (3.47 ppm)-H3 (6.19 ppm) supporting assignment of the major product as the spiroketal corresponding to spirofungin A.
121 (15R): \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 0.85 (d, \(J = 6.6\) Hz, 3H), 0.93 (d, \(J = 6.8\) Hz, 3H), 1.18-1.34 (m, 2H), 1.35-1.47 (m, 3H), 1.55-1.74 (m, 4H), 1.78 (s, 3H), 1.87-2.04 (m, 2H), 2.22 (m, 1H), 2.39 (dd, \(J = 12.1, 6.8\) Hz, 1H), 3.09 (td, \(J = 9.1, 9.1, 2.6\) Hz, 1H), 4.26 (d, \(J = 6.8\) Hz, 2H), 4.81 (d, \(J = 4.1\) Hz, 1H), 5.03-5.09 (m, 2H), 5.59-5.70 (m, 2H), 5.99 (dddd, \(J = 17.0, 9.9, 7.1\) Hz, 1H), 6.23 (d, \(J = 15.8\) Hz, 1H); \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 11.7, 12.7, 17.6, 22.5, 25.6, 29.4, 32.1, 34.8, 36.6, 38.3, 59.6, 73.1, 78.5, 97.8, 116.1, 129.5, 129.8, 134.0, 136.3, 136.5; IR (film): 3407, 2929, 2870, 1641, 1454, 1380, 1222, 1058, 1020, 966 cm\(^{-1}\); ESI-MS: C\(_{20}\)H\(_{32}\)O\(_3\) [M+Na] calc. 343.22, found 343.22; \([\alpha]^{24}_D = +46.1^\circ\) (c = 0.38, CH\(_2\)Cl\(_2\)).

**Methyl ester 122:** To a dry round bottom flask was added spiroketal 120 (0.052 g, 0.16 mmol) and 1.6 mL acetone. Manganese dioxide (0.56 g, 6.5 mmol) was added and the reaction stirred for two hours. The reaction mixture was filtered over Celite, washing with CH\(_2\)Cl\(_2\), then concentrated under reduced pressure. The intermediate aldehyde (~0.16 mmol) was taken up in 1.6 mL MeOH. Sodium cyanide (0.040 g, 0.81 mmol) and acetic acid (0.018 mL, 0.32 mmol) were added. After 2 hours of stirring at room temperature, the reaction was filtered over Celite, washing with ethyl acetate. The organic layer was washed with brine, dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5-10% EtOAc/Hex) to give the product (0.044 g, 78%) as a colorless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 0.75 (d, \(J = 7.2\) Hz, 3H), 0.78 (d, \(J = 6.0\) Hz, 3H), 1.32-1.57 (m, 6H), 1.67-1.81 (m, 3H), 1.89 (m, 1H), 2.19-2.34 (m, 5H), 3.41 (dt, \(J = 9.2, 4.3\) Hz, 1H), 3.71 (s, 3H), 4.15 (dd, \(J = 8.9, 5.1\) Hz, 1H), 4.99-5.08 (m, 2H), 5.79 (s, 1H), 5.88
Methyl ester 123: To a dry round bottom flask was added spiroketal 121 (0.014, 0.04 mmol) and 0.4 mL acetone. Manganese dioxide (0.15 g, 1.72 mmol) was added and the reaction stirred for two hours. The reaction mixture was filtered over Celite, washing with CH$_2$Cl$_2$, then concentrated under reduced pressure. The intermediate aldehyde (~0.04 mmol) was taken up in 0.4 mL MeOH. Sodium cyanide (0.010 g, 0.22 mmol) and acetic acid (0.005 mL, 0.09 mmol) were added. After 2 hours of stirring at room temperature, the reaction was filtered over Celite, washing with ethyl acetate. The organic layer was washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5-10% EtOAc/Hex) to give the product (0.0117 g, 78%) as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 0.85 (d, J= 6.4 Hz, 3H), 0.90 (d, J= 7.1 Hz, 3H), 1.19-1.48 (m, 4H), 1.61-1.84 (m, 4H), 1.88-2.06 (m, 2H), 2.16-2.31 (m, 4H), 2.35-2.44 (m, 1H), 3.10 (dt, J= 9.4, 2.3 Hz, 1H), 3.69 (s, 3H), 4.87 (br. s., 1H) 5.03 (d, J= 10.8 Hz, 1H), 5.09 (d, J= 17.6, 1H), 5.75 (s, 1H) 5.91-6.00 (m, 1H), 6.04 (dd, J= 15.9, 5.4 Hz, 1H), 6.29 (d, J= 15.8 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 11.8, 13.9, 17.6, 22.5, 25.5, 29.4, 31.7, 34.9, 36.5, 38.2, 51.2, 72.5, 78.5, 97.9, 116.2, 118.5, 132.9, 136.3, 136.7, 152.6, 167.8; IR (film): 2949, 2874, 1717, 1614, 1437, 1235, 1157, 1022, 987 cm$^{-1}$; ESI-MS: C$_{21}$H$_{32}$O$_4$ [M+Na] calc. 371.22, found 371.22; [α]$^{25}$D = +51.5° (c = 0.60, CH$_2$Cl$_2$).
**Aldehyde 124:** To a dry 10 mL round bottom flask under argon was added spiroketal 122 (0.026 g, 0.075 mmol) in 0.6 mL degassed CH₂Cl₂ along with freshly distilled methacrolein (32 µL, 0.37 mmol). Grubbs 2nd generation catalyst (0.0032 g, 0.004 mmol) was added in one portion to the solution. The reaction was stirred at reflux for 3 hours then cooled to room temperature and opened to air for 1 hour. The mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography (5-10% EtOAc/Hex) to give the product (0.0216 g, 74%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 0.77 (d, J= 7.2 Hz, 3H), 0.80 (d, J= 6.5 Hz, 3H), 1.30-1.62 (m, 6H), 1.65-1.83 (m, 6H), 1.90 (m, 1H), 2.28 (s, 3H), 2.43-2.53 (m, 1H), 2.54-2.65 (m, 1H), 3.58-3.65 (m, 1H), 3.71 (s, 3H), 4.18 (dd, J= 8.7, 4.9 Hz, 1H), 5.81 (s, 1H), 6.26 (d, J= 15.9 Hz, 1H), 6.44 (dd, J= 15.9, 9.1 Hz, 1H), 6.65 (t, J= 6.8 Hz, 1H), 9.42 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 9.6, 14.5, 16.8, 17.8, 24.3, 27.7, 32.7, 33.2, 34.0, 35.3, 35.6, 51.2, 74.1, 78.4, 96.3, 119.3, 134.8, 136.4, 140.8, 150.8, 151.9, 167.6, 195.3; IR (film): 2929, 2871, 1716, 1688, 1613, 1437, 1235, 1160, 1019, 987 cm⁻¹; ESI-MS: C₂₃H₃₄O₅ [M+Na] calc. 413.23, found 413.23; [α]₂⁵ D = −142.9° (c = 0.38, CH₂Cl₂).

**Aldehyde 125:** To a dry 10 mL round bottom flask under argon was added spiroketal 123 (0.024 g, 0.069 mmol) in 0.6 mL degassed CH₂Cl₂ along with freshly distilled methacrolein (30 µL, 0.34 mmol). Grubbs 2nd generation catalyst (0.003 g, 0.003 mmol) was added in one portion to the solution. The reaction was stirred at reflux for 3 hours then cooled to room temperature and opened to air for 1 hour. The mixture was
concentrated under reduced pressure and the crude product was purified by flash column chromatography (5-10% EtOAc/Hex) to give the product (0.0197 g, 74%) as a colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.88 (d, \(J= 4.2\), 3H), 0.90 (d, \(J= 3.4\) Hz, 3H), 1.21-1.52 (m, 4H), 1.58-1.91 (m, 8H), 2.01 (d, \(J= 14.4\) Hz, 1H), 2.25 (s, 3H), 2.48-2.59 (m, 1H), 2.62-2.72 (m, 1H), 3.26 (dt, \(J= 8.9, 2.7\) Hz, 1H), 3.68 (s, 3H), 4.74 (br. s., 1H), 5.75 (s, 1H), 6.01 (dd, \(J= 15.9, 4.9\) Hz, 1H), 6.26 (d, \(J= 15.6\) Hz, 1H), 6.67 (t, \(J= 6.6\) Hz, 1H), 9.44 (s, 1H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 9.7, 11.8, 13.9, 17.7, 22.6, 25.7, 29.1, 31.6, 33.4, 34.9, 36.4, 51.2, 72.7, 77.8, 98.1, 118.8, 133.0, 136.2, 140.5, 152.2, 152.4, 167.8, 195.4; IR (film): 2951, 2870, 1715, 1687, 1614, 1439, 1236, 1158, 1082, 1020, 987 cm\(^{-1}\); ESI-MS: C\(_{23}\)H\(_{34}\)O\(_5\) [M+Na] calc. 413.23, found 413.23; \([\alpha]\)\(^{25}_D\) = +108.5° (c = 0.12, CH\(_2\)Cl\(_2\)).

**Diene 126:** To a dry round-bottom flask, under argon, was added methylenetriphenylphosphine bromide (0.124 g, 0.347 mmol) in 0.3 mL THF. The mixture was cooled to 0 °C and potassium tert-butoxide (1 M in THF, 0.28 mL, 0.28 mmol) was added. The bright yellow mixture was stirred 30 min at 0 °C upon which the aldehyde 124 (0.021 g, 0.052 mmol) was added in 0.3 mL THF. The reaction was stirred 15 min at 0 °C then quenched with water. The layers were separated and the aqueous layer was extracted with ethyl acetate (2x). The combined organic layers were dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (2-5% EtOAc/Hex) to provide the product as a colorless oil (0.0175 g, 86%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 0.76 (m, 6H), 1.32-1.55 (m, 6H), 1.66-1.84 (m, 6H), 1.90 (br. s., 1H), 2.28 (s, 3H), 2.32 (m, 1H), 2.39 (m, 1H), 3.47 (m, 1H), 3.71 (s, 3H), 4.16 (dd, \(J= 9.1, 5.2\) Hz, 1H), 4.92 (d, \(J= 10.8\) Hz, 1H), 5.08 (d, \(J=...
17.2 Hz, 1H), 5.60 (t, J= 6.8 Hz, 1H), 5.80 (s, 1H), 6.23 (d, J= 15.6 Hz, 1H), 6.40 (dd, J= 17.4, 10.8 Hz, 1H), 6.50 (dd, J= 15.6, 9.2 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 12.1, 14.5, 17.1, 17.8, 24.1, 27.8, 32.1, 33.3, 33.8, 35.7, 36.2, 51.1, 74.7, 78.7, 95.9, 110.4, 119.1, 128.8, 135.1, 135.2, 136.5, 141.9, 152.3, 167.6; IR (film): 2928, 2870, 1718, 1612, 1436, 1235, 1159, 1019, 891 cm$^{-1}$; ESI-MS: C$_{24}$H$_{36}$O$_4$ [M+Na] calc. 411.25, found 411.22; $\alpha^2_{24} = -154.0^\circ$ (c = 0.29, CH$_2$Cl$_2$).

**Diene 127:** To a dry round-bottom flask, under argon, was added methylenetriphenylphosphine bromide (0.102 g, 0.28 mmol) in 0.25 mL THF. The mixture was cooled to 0 °C and potassium tert-butoxide (1 M in THF, 0.23 mL, 0.23 mmol) was added. The bright yellow mixture was stirred 30 min at 0 °C upon which the aldehyde 125 (0.018 g, 0.046 mmol) was added in 0.25 mL THF. The reaction was stirred 15 min at 0 °C then quenched with water. The layers were separated and the aqueous layer was extracted with ethyl acetate (2x). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (2% EtOAc/Hex) to provide the product (0.0134 g, 75%) as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 0.86-0.92 (m, 6H), 1.27-1.35 (m, 1H), 1.36-1.53 (m, 3H), 1.59-1.82 (m, 7H), 1.82 (m, 1H), 2.00 (m, 1H), 2.25-2.34 (m, 4H), 2.51 (m, 1H), 3.13 (td, J= 8.8, 3.0 Hz, 1H), 3.70 (s, 3H), 4.82 (m, 1H), 4.94 (d, J= 10.5 Hz, 1H), 5.09 (d, J= 17.4 Hz, 1H), 5.6 (t, J= 7.0 Hz, 1H), 5.75 (s, 1H), 6.04 (dd, J= 15.8, 5.3 Hz, 1H), 6.28 (d, J= 15.8 Hz, 1H), 6.42 (dd, J= 17.3, 10.6 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 11.8, 12.1, 13.9, 17.8, 22.9, 25.6, 29.0, 31.7, 32.6, 34.6, 36.2, 51.2, 72.5, 78.7, 97.9, 110.7, 118.6, 130.4, 132.9, 135.0, 136.7, 141.8, 152.6.
Cross metathesis product 128: To a dry round bottom flask under argon was added diene 126 (0.018 g, 0.046 mmol) in 0.5 mL degassed CH₂Cl₂ along with alcohol 49 (0.0128 g, 0.069 mmol). A solution of Grubbs 2nd generation catalyst (0.008 g, 0.0092 mmol) in 0.2 mL CH₂Cl₂ was added dropwise to the reaction over 6 hours. Upon completion of catalyst addition, the reaction was stirred for 12 hours at room temperature then opened to air for 1 hour. The mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography (4-20% EtOAc/Hex) to provide recovered diene 126 (0.0059 g, 33%) and the product (0.014 g, 55%) as colorless oils. ¹H NMR (400 MHz, CDCl₃) δ 0.70-0.80 (m, 6H), 1.09 (d, J = 6.5 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.33-1.60 (m, 6H), 1.66-1.97 (m, 4H), 1.72 (s, 3H), 2.20-2.43 (m, 2H), 2.26 (s, 3H), 2.57 (m, 1H), 3.45 (m, 1H) 3.72 (s, 3H) 4.08-4.23 (m, 5H), 5.51 (dd, J = 15.75, 7.40 Hz, 1H), 5.57 (t, J = 6.5 Hz, 1H), 5.80 (s, 1H), 5.87 (d, J = 15.9 Hz, 1H), 6.24 (d, J = 15.9 Hz, 2H), 6.49 (dd, J = 15.6, 9.1 Hz, 1H), 7.01 (dd, J = 15.8, 7.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 13.0, 14.4, 14.5, 14.7, 17.4, 17.8, 23.9, 27.8, 32.5, 33.3, 34.2, 35.9, 36.3, 42.7, 51.3, 60.5, 74.8, 76.3, 78.8, 95.9, 119.1, 122.0, 126.0, 130.0, 133.9, 135.0, 136.7, 137.8, 150.6, 152.6, 166.8, 167.8; IR (film): 3422, 2927, 2862, 1715, 1650, 1367, 1259, 1160, 1029 cm⁻¹; ESI-MS: C₃₂H₄₈O₇ [M+Na] calc. 567.33, found 567.30; [α]²⁴D = -73.0° (c = 0.19, CH₂Cl₂).
Cross metathesis product 129: To a dry round bottom flask under argon was added diene 127 (0.0287 g, 0.074 mmol) in 0.5 mL degassed CH₂Cl₂ along with alcohol 49 (0.0204 g, 0.111 mmol). A solution of Grubbs 2nd generation catalyst (0.0125 g, 0.015 mmol) in 0.25 mL CH₂Cl₂ was added dropwise to the reaction over 6 hours. Upon completion of catalyst addition, the reaction was stirred for 12 hours at room temperature then opened to air for 1 hour. The mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography (4-20% EtOAc/Hex) to provide recovered diene 127 (0.005 g, 17%) and the product (0.0235 g, 58%) as colorless oils. ¹H NMR (500 MHz, CDCl₃): δ 0.88 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 7.1 Hz, 3H), 1.08 (d, J = 6.6 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.36-1.51 (m, 4H), 1.63 (td, J = 12.7, 4.1 Hz, 1H), 1.67-1.84 (m, 7H), 1.85-1.96 (m, 1 H), 1.96-2.03 (m, 1H), 2.23-2.36 (m, 4H), 2.46-2.54 (m, 1H), 2.54-2.63 (m, 1 H), 3.13 (td, J = 8.7, 2.8 Hz, 1H), 3.65-3.74 (m, 3H), 4.12-4.24 (m, 3H), 4.82 (br. s., 1H), 5.52 (dd, J = 15.6, 7.1 Hz,1 H), 5.68 (t, J = 6.8 Hz, 1H), 5.76 (s, 1H), 5.87 (d, J = 15.6 Hz, 1H), 6.04 (dd, J = 15.8, 5.3 Hz, 1H), 6.29 (d, J = 15.8 Hz, 2H), 7.00 (dd, J = 15.8, 7.6 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 11.8, 13.0, 13.9, 14.5, 14.6, 17.8, 22.9, 25.7, 29.0, 31.7, 32.7, 34.6, 36.2, 42.8, 51.2, 60.5, 72.5, 76.2, 78.7, 98.9, 118.6, 122.1, 126.0, 131.1, 132.9, 133.7, 136.6, 137.6, 150.4, 152.6, 166.7, 167.8; IR (film): 3477, 2928, 2862, 1716, 1650, 1453, 1236, 1158, 968 cm⁻¹; ESI-MS: C₃₂H₄₈O₇ [M+Na] calc. 567.33, found 567.30; [α]D²⁴ = +139.3° (c = 0.08, CH₂Cl₂).
(-)-Spirofungin A (1): To a solution of diester 128 (0.0066 g, 0.012 mmol) in THF/H$_2$O/MeOH (300/150/150 µL) was added LiOH (0.004 g, 0.10 mmol). The reaction mixture was stirred for 36 h. The reaction mixture was cooled to 0 °C, and quenched with 1 N HCl, aqueous NH$_4$Cl, and diluted with ethyl acetate. The organic layer was washed with water then brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Et$_2$O: Hex 2:1, 1% AcOH) to give (-)-spirofungin A (0.0053 g, 87%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 0.70-0.82 (m, 6H), 1.11 (d, J = 6.8 Hz, 3H), 1.35 (br. s., 2H), 1.39-1.63 (m, 6H), 1.64-1.83 (m, 7H), 1.93 (br. s., 1H), 2.16-2.42 (m, 5H), 2.56-2.65 (m, 1H), 3.36-3.45 (m, 1H), 4.11-4.21 (m, 2H), 5.46-5.54 (m, 2H), 5.82 (s, 1H), 5.87 (d, J = 15.6 Hz, 1H), 6.21 (d, J = 15.6 Hz, 1H), 6.29 (d, J = 15.6 Hz, 1H), 6.56 (dd, J = 15.6, 9.5 Hz, 1H), 7.11 (dd, J = 15.6, 7.2 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 12.9, 14.3, 14.8, 17.7, 17.8, 23.6, 28.0, 33.3, 33.5, 35.3, 36.5, 36.6, 42.7, 75.0, 76.5, 78.7, 95.8, 118.7, 121.4, 125.5, 130.7, 133.5, 135.6, 137.0, 138.0, 153.3, 154.8, 171.7, 172.2; IR (film): 3419, 2929, 2862, 1698, 1651, 1455, 1380, 1260, 1157, 1020 cm$^{-1}$; ESI-MS: C$_{29}$H$_{42}$O$_7$ [M+Na] calc. 525.28, found 525.25; $[\alpha]_{D}^{24}$ = $-117.9^\circ$ (c = 0.08, CH$_2$Cl$_2$).
(+)-Spirofungin B (2): To a solution of diester 129 (0.0078 g, 0.014 mmol) in THF/H$_2$O/MeOH (350/175/175 μL) was added LiOH (0.0048 g, 0.11 mmol). The reaction mixture was stirred for 36 h. The reaction mixture was cooled to 0 °C, and quenched with 1 N HCl, aqueous NH$_4$Cl, and diluted with ethyl acetate. The organic layer was washed with water then brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Et$_2$O: Hex 2:1, 1% AcOH) to give (+)-spirofungin B (0.0063 g, 88%) as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.85-0.94 (m, 6H), 1.10 (d, $J$= 6.6 Hz, 3H), 1.22-1.35 (m, 3H), 1.36-1.52 (m, 3H), 1.63 (m, 1H), 1.67-1.85 (m, 7H) 1.93 (m, 2H), 2.26 (s, 3H), 2.29-2.41 (m, 1H) 2.45-2.52 (m, 1H), 2.62 (m, 1H), 3.17 (td, $J$= 8.2, 2.5 Hz, 1H), 4.17 (t, $J$= 6.2 Hz, 1H), 4.79 (br. s., 1H), 5.51 (dd, $J$= 15.5, 7.2 Hz, 1H), 5.65 (t, $J$= 6.9 Hz, 1H), 5.78 (s, 1H), 5.87 (d, $J$= 15.8 Hz, 1H), 6.08 (dd, $J$= 15.8, 5.3 Hz, 1H), 6.30 (d, $J$= 15.6 Hz, 2H), 7.10 (dd, $J$= 15.7, 7.5 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 11.8, 13.0, 14.1, 14.9, 17.8, 23.5, 25.7, 28.4, 31.7, 32.6, 34.0, 35.8, 43.0, 72.5, 76.1, 78.6, 97.8, 118.1, 121.4, 125.7, 131.1, 132.9, 134.0, 137.55, 137.64, 153.0, 155.0, 171.2, 171.9; IR (film): 3432, 2941, 2862, 1643, 1454, 1367, 1259, 1020, 967 cm$^{-1}$; ESI-MS: $^{C_{29}}$H$_{42}$O$_7$ [M+Na] calc. 525.28, found 525.25; $[\alpha]^{24}_D$ = +79.0° (c = 0.07, CH$_2$Cl$_2$).
$^{1}H$ NMR SPECTRUM OF 57 (500 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 57 (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 59 (400 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 59 (125 MHz, CDCl$_3$)
$^1\text{H NMR SPECTRUM OF 61 (500 MHz, CDCl}_3\text{)}$
$^{13}$C NMR SPECTRUM OF 61 (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 62 (400 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 62 (100 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 55 (400 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 55 (100 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 64 (500 MHz, CDCl$_3$)
\(^{13}\)C NMR SPECTRUM OF 64 (125 MHz, CDCl\(_3\))
$^1$H NMR SPECTRUM OF THE TES-PROTECTED ALDOL ADDUCT (400 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF THE TES-PROTECTED ALDOL ADDUCT (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 65 (400 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 65 (125 MHz, CDCl$_3$)
\(^1\)H NMR SPECTRUM OF 70 (400 MHz, CDCl\(_3\))
$^{13}$C NMR SPECTRUM OF 70 (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 49 (400 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 49 (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 110 (500 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 110 (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF THE TES-PROTECTED ALDOL ADDUCT (400 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF THE TES-PROTECTED ALDOL ADDUCT (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 111 (400 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 111 (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF THE $\alpha,\beta$-UNSATURATED ESTER (400 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF THE $\alpha,\beta$-UNSATURATED ESTER (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF THE ETHYL ESTER (400 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF THE ETHYL ESTER (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 112 (400 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 112 (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF THE $\alpha,\beta$-UNSATURATED KETONE (500 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF THE $\alpha,\beta$-UNSATURATED KETONE (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 113 (400 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 113 (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 120 (500 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 120 (125 MHz, CDCl$_3$)
\(^1\text{H NMR SPECTRUM OF 121 (500 MHz, CDCl}_3\)
$^{13}$C NMR SPECTRUM OF 121 (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 122 (500 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 122 (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 123 (500 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 123 (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 124 (400 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 124 (100 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 125 (400 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 125 (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 126 (500 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 126 (100 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 127 (500 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 127 (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 128 (400 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 128 (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 129 (500 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 129 (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF (−)-SPIROFUNGIN A (1) (400 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF (−)-SPIROFUNGIN A (I) (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF (+)-SPIROFUNGIN B (2) (500 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF (+)-SPIROFUNGIN B (2) (125 MHz, CDCl$_3$)
CHAPTER SIX

Experimental and NMR Spectra: (+)-Sorangicin A

6.1 Materials and Methods

Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer and values reported in cm$^{-1}$. Proton and carbon nuclear magnetic resonance spectra were acquired on a Bruker model Avance 400 ($^1$H at 400 MHz; $^{13}$C at 100 MHz, CDCl$_3$), Bruker model Avance 500 ($^1$H at 500 MHz; $^{13}$C at 125 MHz, CDCl$_3$), or Bruker model Avance 600 ($^1$H at 600 MHz; $^{13}$C at 150 MHz, CDCl$_3$). Chemical shifts are reported relative to chloroform, $\delta$ 7.26 for $^1$H NMR spectra and $\delta$ 77.2 for $^{13}$C NMR spectra. Optical rotations were determined using a Jasco P1010 polarimeter. Mass spectra were obtained using a Bruker BioTOF II mass spectrometer with electrospray ionization (ESI). Thin layer chromatography (TLC) was conducted on silica gel F254 TLC plates purchased from Scientific Adsorbents, Inc. Flash column chromatography was carried out using Ultra Pure Silica Gel Silia-P(40 to 63 $\mu$m) purchased from SiliCycle Inc. The second generation Grubbs precatalyst (G2) is defined as [Ru=CHPh(Cl)$_2$(PCy$_3$)(DHIMes)]. Diethyl ether (Et$_2$O), tetrahydrofuran (THF), dichloromethane (CH$_2$Cl$_2$), and toluene were dried by being passed through a column of neutral alumina under nitrogen immediately prior to use. Alkylamines were distilled from
calcium hydride immediately prior to use. All other reagents and solvents were used as received from the manufacturer, unless otherwise specified. All air and water sensitive reactions were performed in flasks flame dried under positive flow argon and conducted under an argon atmosphere.

6.2 Experimental procedures

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\text{p-Methoxy benzyl protected bicyclic ether 263:}
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To a dry round bottom flask under argon was added bicyclic ether 227 (0.37 g, 1.41 mmol) in 6.0 mL THF: DMF (1:1). The reaction was cooled to 0 °C and sodium hydride (60% in mineral oil, 0.17 g, 4.24 mmol) was added in one portion. The reaction was stirred for 30 minutes, then p-methoxybenzyl bromide (0.31 mL, 2.12 mmol) was added. After 2 hours stirring at 0 °C, the reaction mixture was diluted with ethyl acetate and quenched with water. The layers were separated and the aqueous layer extracted three times with ethyl acetate. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10% EtOAc/Hex) to provide the product (0.506 g, 94%) as a colorless oil.

\[^1\text{H NMR (600 MHz, CDCl}_3] \delta 7.38 (m, 2H), 7.28-7.34 (m, 4H), 7.21-7.26 (m, 1H), 6.89 (d, J= 8.7, 2H), 6.52 (d, J= 15.8, 1H), 6.11 (dd, J= 15.6, 7.7 Hz, 1H), 4.59 (d, J= 11.7 Hz, 1H), 4.56 (d, J= 11.7 Hz, 1H), 4.42 (br. s., 1H), 4.30 (d, J= 6.4 Hz, 1H), 4.10-4.15 (m, 1H), 3.98 (t, J= 8.5 Hz, 1H), 3.84 (d, J= 6.0 Hz, 2H), 3.77-3.82 (m, 3H), 2.05 (ddd, J= 11.5, 6.6, 2.6 Hz, 1H), 1.92 (d, J= 10.9 Hz, 1H), 1.47-1.54 (m, 1H), 0.92 (d,
$J=6.8 \text{ Hz, } 3\text{H})$; $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 159.4, 136.7, 132.6, 130.5, 129.6, 129.3, 128.7, 127.9, 126.7, 113.9, 81.9, 79.8, 79.1, 75.1, 73.1, 67.7, 55.4, 41.9, 38.9, 15.4; IR (film): 2961, 2933, 2873, 1612, 1513, 1451, 1248, 1075, 967, 820; ESI-MS: C$_{24}$H$_{28}$O$_4$ [M+Na]$\text{calc.}$ 403.19, found 403.2; $[\alpha]^{23}_D = -41.9 \ (c = 0.48, \text{CH}_2\text{Cl}_2)$.

Bicyclic ether 264: To a dry round bottom flask under argon was added PMB protected bicyclic ether 263 (0.400 g, 1.05 mmol) in 20 mL THF: pH 7 buffer (1:1). Osmium tetroxide (20 mg/mL in water, 1.34 mL, 0.11 mmol) was added dropwise followed by sodium periodate (0.449 g, 2.10 mmol). The reaction was stirred for 2 hours then quenched with 1:1 NaHCO$_3$:Na$_2$S$_2$O$_3$. The layers were separated and the aqueous layer extracted three times with ethyl acetate. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude aldehyde was used immediately in the next reaction without further purification.

To a dry round-bottom flask, under argon, was added methylenetriphenylphosphine bromide (1.88 g, 5.26 mmol) in 8.0 mL THF. The mixture was cooled to 0 °C and potassium tert-butoxide (1 M in THF, 4.20 mL, 4.20 mmol) was added. The bright yellow mixture was stirred 30 min at 0 °C at which time the aldehyde was added in 2.5 mL THF. The reaction was stirred 1 hour at 0 °C then quenched with water. The layers were separated and the aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (20% EtOAc/Hex) to provide the product as a colorless oil (0.278 g,
87% over 2 steps. \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.29 (d, \(J = 8.7\) Hz, 2H), 6.87 (d, \(J = 8.3\) Hz, 2H), 5.74 (ddd, \(J = 17.2, 10.1, 7.3\) Hz, 1H), 5.19 (d, \(J = 17.0\) Hz, 1H), 5.14 (d, \(J = 10.5\) Hz, 1H), 4.54 (q, \(J = 11.7\) Hz, 2H), 4.38 (br. s., 1H), 4.25 (d, \(J = 6.4\) Hz, 1H), 4.07-4.11 (m, 1H), 3.77-3.82 (m, 6H), 2.01 (ddd, \(J = 11.6, 6.9, 2.6\) Hz, 1H), 1.86 (d, \(J = 11.6\) Hz, 1H), 1.37-1.43 (m, 1H), 0.88 (d, 6.8 Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 159.3, 138.1, 130.5, 129.6, 117.3, 113.9, 81.9, 80.1, 79.0, 75.0, 73.1, 67.8, 55.4, 41.4, 38.8, 15.2; IR (film): 2934, 2874, 1613, 1514, 1302, 1248, 1076, 822; ESI-MS: C\(_{18}\)H\(_{24}\)O\(_4\) [M+Na] calc.327.16, found 327.2; \([\alpha]_{D}^{23} = -63.7^\circ\) (\(c = 0.30\), CH\(_2\)Cl\(_2\)).

Aldehyde 278:

To a dry round bottom flask under argon was added protected aldol adduct 240 (1.35 g, 3.0 mmol) in 30 mL CH\(_2\)Cl\(_2\). The yellow solution was cooled to –78 °C and DIBAL (1M in hexanes) was added dropwise via syringe until the reaction mixture became colorless (6.0 mL, 6.0 mmol). The reaction mixture was immediately quenched with saturated potassium sodium tartrate, warmed to room temperature, and vigorously stirred for 2 hours. The layers were separated and the aqueous layer extracted twice with CH\(_2\)Cl\(_2\). The combined organic layers were dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5-10% EtOAc/Hex) to provide the product (0.602 g, 83%) as a colorless oil. \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 9.56 (s, 1H), 5.75 (ddt, \(J = 17.2, 10.1, 7.3\) Hz, 1H), 5.04-5.13 (m, 2H), 4.20 (td, \(J = 6.6, 3.8\) Hz, 1H), 2.46 (qd, \(J = 6.8, 3.8\) Hz, 1H), 2.29 (t, \(J = 7.0\) Hz, 2H), 1.09 (d, \(J = 7.2\) Hz, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 205.3, 134.3, 118.2, 71.5, 51.0, 39.7, 25.9, 18.2, 7.6, -4.0, -4.6; IR (film): 2955, 2930,
2858, 1730, 1472, 1036, 838, 776; ESI-MS: C_{13}H_{26}O_{2}Si [M+H] calc. 243.17, found 243.2; 
$\alpha^2_2 = -29.1^\circ$ (c = 0.95, CH$_2$Cl$_2$).

Cross metathesis product 242:

To a dry round bottom flask under argon was added aldehyde 278 (0.63 g, 2.60 mmol) in 22 mL degassed toluene along with diacetate 274 (1.12 g, 6.50 mmol). Grubbs 2nd generation catalyst (0.110 g, 0.13 mmol) was added in one portion to the solution. The reaction was stirred at room temperature for 12 hours then opened to air for 1 hour. The mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography (12-15% EtOAc/Hex) to give the product (0.544 g, 67%) as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 9.74 (s, 1H), 5.67-5.73 (m, 1H), 5.60-5.66 (m, 1H), 4.51 (d, J= 6.0 Hz, 2H), 4.18 (td, J= 6.4, 3.8 Hz, 1H), 2.44 (qd, J= 6.8, 3.8 Hz, 1H), 2.26-2.31 (m, 2H), 2.06 (s, 3H), 1.08 (d, J= 7.2 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 204.9, 170.8, 131.1, 127.3, 71.4, 64.7, 51.0, 37.9, 25.7, 21.0, 18.0, 7.7, -4.3, -4.8.

Cross metathesis product 281:

To bicyclic ether 264 (0.126 g, 0.41 mmol) in 1.5 mL degassed toluene at room temperature was added tetrahydropyran 228 (0.154 g, 0.28 mmol) dropwise over 6
hours as a solution in 0.5 mL toluene via syringe pump. Grubbs 2nd generation catalyst (0.023 g, 0.028 mmol) was added in three portions as a solution in 0.3 mL toluene. Upon completion of addition of tetrahydropyran 228, the reaction was stirred for 12 hours at room temperature, then opened to air and stirred 1 hour. The reaction mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography (10-20% EtOAc/Hex) to give the product (0.177 g, 77%) as a colorless oil. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 0.01 (s, 3H), 0.02 (s, 3H), 0.56-0.63 (m, 12H), 0.82-0.86 (m, 6H), 0.87 (s, 9H), 0.95 (t, $J$ = 7.9 Hz, 18H), 1.34-1.41 (m, 2H), 1.42 - 1.49 (m, 1H), 1.64-1.72 (m, 1H), 1.85 (d, $J$ = 11.7 Hz, 1H), 1.95-2.06 (m, 2H), 2.23-2.31 (m, 1H), 3.46 (dd, $J$ = 10.2, 6.0 Hz, 1H), 3.57 (dd, $J$ = 10.2, 5.7 Hz, 1H), 3.69 (q, $J$ = 5.5 Hz, 1H), 3.74-3.83 (m, 4H), 3.80 (s, 3H), 3.83-3.89 (m, 2H), 4.08 (td, $J$ = 5.6, 1.7 Hz, 1H), 4.24 (d, $J$ = 6.8 Hz, 1H), 4.35 (br. s., 1H), 4.51 (d, $J$ = 11.3 Hz, 1H), 4.56 (d, $J$ = 11.7 Hz, 1H), 5.41 (dd, $J$ = 15.4, 7.9 Hz, 1H), 5.60 (ddd, $J$ = 14.9, 9.2, 5.3 Hz, 1H), 6.87 (d, $J$ = 8.3 Hz, 2H), 7.29 (d, $J$ = 8.3 Hz, 2H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 159.4, 131.4, 131.2, 130.5, 129.6, 113.9, 82.0, 80.0, 79.1, 76.1, 75.0, 73.6, 73.12, 73.05, 71.3, 68.1, 64.6, 55.4, 41.7, 38.9, 38.4, 35.8, 28.9, 26.0, 18.3, 15.3, 10.8, 7.1, 7.0, 5.2, 4.5, –4.6, –4.8; IR (film): 2954, 2876, 1613, 1514, 1460, 1302, 1248, 1078; ESI-MS: C$_{45}$H$_{82}$O$_{8}$Si$_{3}$ [M+Na] calc. 857.52, found 857.4; [$\alpha$]$^{23}_D$ = –7.2° ($c$ = 0.29, CH$_2$Cl$_2$).

**Aldehyde 282:**

To a dry round bottom flask under argon was added freshly distilled oxalyl chloride (neat, 41 $\mu$L, 0.48 mmol) in 0.25 mL dichloromethane. The solution was cooled to –78 °C and
DMSO (70 µL, 0.97 mmol) in 0.25 mL CH₂Cl₂ was added dropwise. After stirring 15 minutes, bis-TES ether 281 (0.081 g, 0.10 mmol) in 0.25 mL CH₂Cl₂ was added dropwise. The reaction mixture was stirred for 15 minutes at −78 °C then allowed to warm to −40 °C and stirred for 1 hour. Upon recooling to −78 °C, triethylamine (0.24 mL, 1.75 mmol) was added slowly. The reaction was allowed to come to room temperature over two hours, then diluted with CH₂Cl₂ and quenched with water. The aqueous layer was extracted twice with CH₂Cl₂, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (5-10-20% EA/Hex to give the product (0.054 g, 78%) as a colorless oil.

\(^1\)H NMR (500 MHz, CDCl₃) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.62 (q, J = 7.9 Hz, 6H), 0.83-0.85 (m, 6H), 0.87 (s, 9H), 0.95 (t, J = 8.0 Hz, 9H), 1.31 (d, J = 13.6 Hz, 1H), 1.37 (dd, J = 9.1, 6.9 Hz, 1H), 1.48 (d, J = 6.9 Hz, 1H), 1.78 (td, J = 13.4, 2.2 Hz, 1H), 1.84 (d, J = 11.4 Hz, 1H), 1.95-2.06 (m, 2H), 2.23-2.31 (m, 1H), 3.76 (t, J = 8.5 Hz, 1H) 3.78-3.81 (m, 2H), 3.79 (s, 3H), 3.83 - 3.87 (m, 1H), 3.90 (td, J = 7.3, 1.6 Hz, 1H), 3.95 (dd, J = 4.7, 1.0 Hz, 1H), 4.02 (ddd, J = 11.7, 4.7, 1.9 Hz, 1H), 4.05-4.10 (m, 1H), 4.24 (d, J = 6.6 Hz, 1H), 4.34 (br. s., 1H), 4.54 (q, J = 11.7 Hz, 2H), 5.40 (dd, J = 15.3, 7.7 Hz, 1H), 5.56 (ddd, J = 14.8, 8.2, 5.4 Hz, 1H), 6.86 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 9.62 (d, J = 1.3 Hz, 1H); \(^{13}\)C NMR (150 MHz, CDCl₃): δ 203.3, 159.4, 131.7, 130.6, 130.5, 129.6, 113.9, 82.0, 80.2, 79.8, 79.1, 75.0, 74.2, 73.9, 73.1, 70.8, 60.0, 55.5, 41.7, 38.9, 38.3, 35.5, 30.0, 26.0, 18.2, 15.3, 10.8, 6.9, 5.0, −4.7, −4.8; IR (film): 2955, 2876, 1737, 137, 1614, 1514, 1302, 1250, 1077, 836, 775; ESI-MS: C₃₉H₆₆O₈Si₂ [M+Na] calc. 741.42, found 741.3; [α]²¹_D = −6.6° (c = 0.25, CH₂Cl₂).
Vinyl addition product 286:

To a flame-dried round bottom flask under argon was added vinyl iodide (0.133 g, 0.41 mmol) and 0.8 mL THF. Upon cooling the solution to −78 °C, tert-butyllithium (1.7 M in pentane, 0.50 mL, 0.84 mmol) was added dropwise. The reaction was stirred for 1.5 h then dimethyl zinc (1.0 M in heptanes, 0.61 mL, 0.61 mmol) was added dropwise and stirred an additional 15 minutes at −78 °C, at which time aldehyde 282 (0.098 g, 0.14 mmol) in 0.6 mL THF was added dropwise. After three hours stirring, the reaction was quenched with saturated ammonium chloride and diluted with ether. The aqueous phase was extracted three times with ether, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (10-15% EA/Hex to give the product (0.103 g, 82%) as a colorless oil.

$^1$H NMR (600 MHz, CDCl$_3$) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.04 (s, 6H), 0.61 (q, $J$= 8.2 Hz, 6H), 0.82-0.86 (m, 6H), 0.87 (s, 9H), 0.89 (s, 9H), 0.95 (t, $J$= 7.9 Hz, 9H), 1.34-1.42 (m, 1H), 1.43-1.50 (m, 1H), 1.53-1.66 (m, 4H), 1.84 (d, $J$= 10.9 Hz, 1H), 1.96-2.02 (m, 1H), 2.02-2.12 (m, 3H), 2.22-2.30 (m, 1H), 2.85 (d, $J$= 3.0 Hz, 1H), 3.55 (t, $J$= 5.7 Hz, 1H), 3.61 (t, $J$= 6.4 Hz, 2H), 3.74-3.85 (m, 5H), 3.79 (s, 3H), 3.86-3.92 (m, 1H), 4.05-4.09 (m, 1H), 4.10-4.15 (m, 1H), 4.23 (d, $J$= 6.8 Hz, 1H), 4.35 (br. s., 1H), 4.51 (d, $J$= 11.3 Hz, 1H), 4.56 (d, $J$= 11.7 Hz, 1 H), 5.43 (dd, $J$= 15.3, 7.3 Hz, 1H), 5.51 (dd, $J$= 15.4, 7.2 Hz, 1H), 5.57 (ddd, $J$= 14.7, 7.5, 5.7 Hz, 1H), 5.67-5.74 (m, 1H), 6.86 (d, $J$= 8.3 Hz, 2H), 7.28 (d, $J$= 8.3 Hz, 2H); $^{13}$C NMR (150 MHz, CDCl$_3$): δ 159.3, 133.0, 131.9, 130.5, 130.3,
129.6, 129.4, 113.9, 82.0, 79.7, 79.1, 77.7, 75.6, 75.01, 74.98, 73.8, 73.1, 71.0, 68.0, 62.9, 55.4, 41.7, 38.9, 38.2, 35.7, 32.5, 30.7, 29.0, 26.1, 26.0, 18.5, 18.2, 15.4, 10.8, 7.2, 62.9, 55.4, 41.7, 38.9, 38.2, 35.7, 32.5, 30.7, 29.0, 26.1, 26.0, 18.5, 18.2, 15.4, 10.8, 7.2, 5.4, −4.7, −4.8, −5.1; IR (film): 3436, 2954, 2931, 1614, 1514, 1251, 1099, 836, 775; ESI-MS: C_{50}H_{90}O_{9}Si_{3} [M+Na] calc. 941.58, found 941.5; [α]_{D}^{23} = −9.9° (c = 1.68, CH_{2}Cl_{2}).

**Aldehyde 293:**

To a dry round bottom flask under argon was added mixed acetal 249 (0.208 g, 0.45 mmol) and tert-butyldimethyl silyl vinyl ether (0.214 g, 1.35 mmol). A solution of lithium perchlorate (3 M in ethyl acetate, 4.50 mL, 13.5 mmol) was added to the reaction. The reaction was stirred at room temperature for two hours then quenched with water. The layers were separated and the aqueous layer extracted three times with CH_{2}Cl_{2}. The combined organic layers were washed with water then brine, dried over Na_{2}SO_{4}, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (15-30% EtOAc/Hex) to provide the product (0.169 g, 82%) as a colorless oil. 

$^1$H NMR (600 MHz, CDCl$_3$) δ 0.92 (d, J = 6.4 Hz, 3H), 1.17-1.37 (m, 6H), 1.55-1.62 (m, 2H), 1.67 (s, 3H), 2.33-2.44 (m, 1H), 2.54 (ddd, J = 16.4, 5.1, 1.5 Hz, 1H), 2.79 (ddd, J = 16.5, 8.9, 2.6 Hz, 1H), 3.34 (s, 3H), 3.42 (t, J = 6.6 Hz, 2H), 3.76-3.83 (m, 3H), 3.96 (dd, J = 5.3, 2.3 Hz, 1H), 4.06 (s, 1H), 4.42 (s, 2H), 4.58 (d, J = 6.8 Hz, 1H), 4.68 (d, J = 6.8 Hz, 1H), 4.93 (td, J = 5.6, 2.5 Hz, 1H), 5.34 (d, J = 9.4 Hz, 1H), 5.92 (dd, J = 10.2, 3.0 Hz, 1H), 6.09 (ddd, J = 10.0, 5.2, 2.1 Hz, 1H), 6.87 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.7 Hz, 3H), 9.79 (s, 1H); $^{13}$C NMR (150 MHz, CDCl$_3$): δ 200.7, 159.2, 133.4, 131.7, 131.0, 129.40, 129.37, 126.3, 113.9, 96.1, 74.9, 72.7, 70.4, 68.8, 68.6, 55.7, 55.4,
46.2, 37.6, 32.1, 29.9, 27.5, 26.5, 21.0, 14.1; IR (film): 2929, 2854, 1726, 1613, 1513, 1248, 1101, 1038; ESI-MS: C_{27}H_{40}O_{6} [M+Na] calc. 483.27, found 483.3; [α]^{23}_{D} = 92.0° (c = 0.70, CH_{2}Cl_{2}).

Alcohol 294:

To a dry round bottom flask under argon was added aldehyde 293 (0.375 g, 0.81 mmol) in 7 mL anhydrous methanol. Sodium borohydride (0.037 g, 0.98 mmol) was added and the reaction stirred for 1 hour. The reaction was quenched with sat. ammonium chloride and dilute with CH_{2}Cl_{2}. The layers were separated and the aqueous layer extracted three times with CH_{2}Cl_{2}. The combined organic layers were washed with saturated NaCl, dried over Na_{2}SO_{4}, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (30-50% EtOAc/Hex) to provide the product (0.365 g, 97%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 0.95 (d, J= 6.9 Hz, 3H), 1.19 - 1.39 (m, 6H), 1.54-1.65 (m, 2H), 1.70 (s, 3H), 1.97-2.09 (m, 1H), 2.35-2.48 (m, 1H), 2.82 (dd, J= 9.1, 2.2 Hz, 1H), 3.36 (s, 3H), 3.44 (t, J= 6.6 Hz, 2H), 3.74 - 3.85 (m, 1H), 3.82 (s, 3H), 3.85-3.94 (m, 1H), 3.99 (dd, J= 5.4, 1.9 Hz, 1H), 4.14 (s, 1H), 4.44 (s, 2H), 4.59 (d, J= 6.9 Hz, 1H), 4.58-4.64 (m, 1H), 4.70 (d, J= 6.9 Hz, 1H), 5.42 (d, J= 9.5 Hz, 1H), 5.92 (dd, J= 10.2, 3.2 Hz, 1H), 6.08 (ddd, J= 10.1, 5.4, 1.9 Hz, 1H), 6.89 (d, J= 8.8 Hz, 2H), 7.28 (d, J= 8.2 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 159.2, 133.2, 133.0, 131.0, 129.6, 129.4, 125.0, 113.9, 95.9, 74.5, 74.0, 72.6, 70.4, 67.8, 62.2, 55.7, 55.4, 37.6, 33.2, 32.1, 29.9, 27.5, 26.5, 12.1, 14.3; IR (film): 3434, 2928,
1643, 1513, 1248, 1100, 1038; ESI-MS: C_{27}H_{42}O_{6} \ [M+Na] \ \text{calc.} \ 485.29, \ \text{found} \ 485.3; \ [\alpha]^{23}_{D} = 88.7^\circ \ (c = 0.68, \ \text{CH}_2\text{Cl}_2).

\[ \text{Diol:} \]

Alcohol 294 (0.040 g, 0.086 mmol) was taken up in 0.9 mL 15% HCl in tert-butyl alcohol at room temperature. After two hours stirring, the reaction was diluted with diethyl ether and quenched with sat. sodium bicarbonate. The layers were separated and the aqueous layer extracted three times with diethyl ether. The combined organic layers were dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (50-75% EtOAc/Hex) to provide the product (0.031 g, 86%) as a colorless oil. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 0.95 (d, $J$ = 6.8 Hz, 3H), 1.20-1.28 (m, 3H), 1.28-1.37 (m, 3H), 1.53-1.62 (m, 2H), 1.67 (s, 3H), 1.98-2.06 (m, 1H), 2.39-2.48 (m, 1H), 2.62 (dd, $J$ = 9.0, 2.6 Hz, 1H), 3.42 (t, $J$ = 6.59 Hz, 2H), 3.74-3.79 (m, 1H), 3.80 (s, 3H), 3.82-3.89 (m, 1H), 3.90-3.95 (m, 1H), 4.12 (s, 1H), 4.42 (s, 2H), 4.52-4.58 (m, 1H), 5.41 (d, $J$ = 9.8 Hz, 1H), 5.87 (dd, $J$ = 10.0, 3.2 Hz, 1H), 6.09 (ddd, $J$ = 10.0, 5.7, 1.9 Hz, 1H), 6.87 (d, $J$ = 8.7 Hz, 2H), 7.26 (d, $J$ = 8.3 Hz, 2H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 159.2, 133.4, 132.7, 131.0, 129.6, 129.4, 126.6, 113.9, 74.6, 73.9, 72.6, 70.4, 62.13, 62.06, 55.5, 37.6, 33.1, 32.1, 29.9, 27.4, 26.5, 21.4, 14.4; IR (film): 3418, 2928, 2856, 1613, 1513, 1248, 1089, 1035; ESI-MS: C_{25}H_{38}O_{5} \ [M+Na] \ \text{calc.} \ 441.26, \ \text{found} \ 441.2; \ [\alpha]^{23}_{D} = 77.8^\circ \ (c = 0.19, \ \text{CH}_2\text{Cl}_2).
Bis-TBS dihydropyran 295:

To a dry round bottom flask under argon was added the diol (0.031 g, 0.07 mmol) and 1.5 mL CH$_2$Cl$_2$. Upon cooling the solution to $-78$ °C, 2,6-lutidine (0.05 mL, 0.44 mmol) was added slowly, followed by TBSOTf (0.05 mL, 0.22 mmol). The reaction was stirred 1 hour at $-78$ °C then quenched with saturated sodium bicarbonate. The layers were separated and the aqueous layer extracted three times with methylene chloride. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexanes to 5% EtOAc/Hex) to provide the product (0.048 g, 99%) as a colorless oil. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 0.03 (s, 3H), 0.04 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.92 (d, $J= 6.8$ Hz, 3H), 1.18-1.35 (m, 6H), 1.56-1.60 (m, 2H), 1.61-1.66 (m, 1H), 1.66 (s, 3H), 1.75-1.85 (m, 1H), 2.31-2.42 (m, 1H), 3.42 (t, $J= 6.8$ Hz, 2H), 3.67-3.77 (m, 2H), 3.80 (s, 3H), 3.97 (br. s., 1H), 4.08 (t, $J= 3.6$ Hz, 1H), 4.34-4.40 (m, 1H), 4.43 (s, 2H), 5.34 (d, $J= 9.4$ Hz, 1H), 5.78 (dd, $J= 10.2, 2.6$ Hz, 1H), 5.85 (ddd, $J= 10.2, 4.5, 2.2$ Hz, 1H), 6.87 (d, $J= 8.3$ Hz, 2H), 7.26 (d, $J= 8.7$ Hz, 2H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 159.3, 133.2, 132.4, 131.0, 130.2, 129.4, 127.3, 113.9, 76.2, 72.7, 70.4, 69.3, 65.6, 60.2, 55.5, 37.8, 35.4, 32.1, 30.1, 27.6, 26.6, 26.2, 26.1, 21.1, 18.5, 18.4, 14.4, $-3.9$, $-4.2$, $-5.1$, $-5.2$; IR (film): 2928, 2856, 1613, 1514, 1463, 1360, 1302, 1250, 1172, 1099, 1039, 836, 775; ESI-MS: C$_{37}$H$_{66}$O$_5$Si$_2$ [M+Na] calc. 669.43, found 669.3; $[\alpha]^{23}_D = 68.7^\circ$ (c = 0.50, CH$_2$Cl$_2$).
Alcohol:

To a solution of bis-TBS dihydropyran 295 (0.152 g, 0.23 mmol) in CH₂Cl₂ (4.7 mL) and pH 7 buffer (0.6 mL) at 0 °C was added DDQ (0.133 g, 0.59 mmol). After 1 hour, the reaction mixture was quenched with sat. NaHCO₃, and diluted with water and CH₂Cl₂. The layers were separated and the aqueous layer extracted three times with methylene chloride. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5-10% EtOAc/Hex) to provide 0.172 g of a mixture of the alcohol and 4-methoxybenzaldehyde which was used in the next reaction without further purification. Further flash column chromatography afforded the clean product for characterization: ¹H NMR (600 MHz, CDCl₃) δ 0.03 (s, 3H), 0.04 (s, 9H), 0.85 (s, 9H), 0.88 (s, 9H), 0.93 (d, J= 6.8 Hz, 3H), 1.17-1.36 (m, 6H), 1.50-1.58 (m, 2H), 1.60-1.71 (m, 1H), 1.66 (s, 3H), 1.75-1.86, (m, 1H), 2.34-2.44 (m, 1H), 3.57-3.66 (m, 2H), 3.66-3.78 (m, 2H) 3.97 (br. s., 1H), 4.09 (t, J= 3.6 Hz, 1H), 4.33-4.40 (m, 1H), 5.35 (d, J= 9.4 Hz, 1H), 5.78 (dd, J= 10.2, 3.0 Hz, 1H), 5.85 (ddd, J= 10.2, 4.5, 1.9 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 133.1, 132.4, 130.1, 127.3, 76.2, 69.3, 65.5, 63.3, 60.2, 37.8, 35.4, 33.0, 32.1, 27.5, 26.2, 26.13, 26.10, 18.5, 18.4, 14.4, −3.9, −4.3, −5.1, −5.2; IR (film): 3366, 2928, 2857, 1471, 1389, 1361, 1254, 1100, 836, 775; ESI-MS: CₓHᵧO₀Si₂ [M+Na] calc. 549.38, found 549.4; [α]²³_D = 72.0° (c = 0.41, CH₂Cl₂).
Aldehyde 296:

To a dry round bottom flask under argon was added 0.172 g of the alcohol (as a 1:1 mixture with 4-methoxybenzaldehyde) and 5.0 mL CH$_2$Cl$_2$. Upon cooling to 0 °C, pyridine (0.10 mL, 1.30 mmol) and Dess-Martin periodinane (0.22 g, 0.52 mmol) were added successively. The reaction was warmed to room temp. After two hours stirring, an additional portion of Dess-Martin periodinane was introduced to the reaction mixture. The reaction was stirred at room temperature an additional two hours then quenched with sat. sodium bicarbonate. The layers were separated and the aqueous layer extracted three times with methylene chloride. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (3-5% EtOAc/Hex) to provide the product (0.118 g, 87% over 2 steps) as a colorless oil.  

$^1$H NMR (600 MHz, CDCl$_3$) δ; 0.02 (s, 3H), 0.04 (s, 9H), 0.88 (s, 9H), 0.85 (s, 9H), 0.93 (d, $J$= 6.8 Hz, 3H), 1.20-1.34 (m, 4H), 1.53-1.69 (m, 3H), 1.65 (s, 3H), 1.76-1.84 (m, 1H), 2.34-2.43 (m, 3H), 3.66-3.76 (m, 2H), 3.96 (br. s., 1H), 4.09 (t, $J$= 3.6 Hz, 1H), 4.34-4.40 (m, 1H), 5.34 (d, $J$= 9.8 Hz, 1H), 5.78 (dd, $J$= 10.2, 2.6 Hz, 1H), 5.85 (ddd, $J$= 10.2, 4.7, 2.1 Hz, 1H), 9.75 (s, 1H); $^{13}$C NMR (150 MHz, CDCl$_3$): δ 203.0, 132.7, 132.4, 130.4, 127.3, 76.1, 69.3, 65.3, 60.2, 44.1, 37.5, 35.4, 32.0, 27.3, 26.16, 26.12, 22.5, 21.1, 18.5, 18.4, 14.4, −3.8, −4.2, −5.1, −5.2; IR (film): 2954, 2857, 1729, 1463, 1389, 1254, 1100; ESI-MS: C$_{29}$H$_{56}$O$_3$Si$_2$ [M+Na] calc. 547.36, found 547.4; $[\alpha]^{23}_D$ = 91.4° (c =0.14, CH$_2$Cl$_2$).
tert-Butyl ester 162:

To a solution of aldehyde 296 (0.070 g, 0.13 mmol) in tert-butanol (1.2 mL) and pH 4 phosphate buffer (0.67 mL) was added 2-methyl-2-butene (0.57 mL, 5.3 mmol) and sodium chlorite (0.060 g, 0.67 mmol) successively. The reaction was stirred at room temperature for 2 hours then quenched with sat. ammonium chloride. The layers were separated and the aqueous layer extracted three times with ethyl acetate. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford the crude carboxylic acid which was used in the next reaction without further purification.

To a solution of the crude carboxylic acid in dichloromethane (0.5 mL) was added tert-butyl isourea 159 (0.13 g, 0.65 mmol, 5.0 equiv). After stirring at room temperature for 24 h an additional 5.0 equiv of isourea 159 were added. The reaction was stirred an additional 12 h, then diluted with methylene chloride and quenched with water. The layers were separated and the aqueous layer extracted three times with methylene chloride. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10% EtOAc/Hex) to provide the product (0.066 g, 83%) as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.05 (s, 6H), 0.86 (s, 9H), 0.88 (s, 9H), 0.93 (d, J= 6.6 Hz, 3H), 1.19-1.33 (m, 4H), 1.44 (s, 9H), 1.50-1.59 (m, 3H), 1.65 (s, 3H), 1.76-1.85 (m, 1H), 2.18 (t, J= 7.6 Hz, 2H), 2.34-2.43 (m, 1H), 3.66-3.77 (m, 2H), 3.96 (br. s., 1H), 4.08 (t, J= 3.5 Hz, 1H), 4.36 - 4.40 (m, 1H), 5.34 (d, J=
9.1 Hz, 1H), 5.79 (dd, J = 10.4, 2.8 Hz, 1H), 5.85 (ddd, J = 10.1, 4.7, 1.9 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 173.5, 133.0, 132.4, 130.3, 127.3, 80.0, 76.2, 69.4, 65.5, 60.2, 37.5, 35.8, 35.4, 32.0, 28.3, 27.2, 26.2, 26.1, 25.5, 21.1, 18.6, 18.4, 14.4, −3.8, −4.2, −5.1, −5.2; IR (film): 2928, 2857, 1732, 1643, 1461, 1390, 1366, 1254, 1099, 836, 775; $[\alpha]^{23}$D = 74.4° (c = 0.12, CH$_2$Cl$_2$).

**Alcohol 297:**

To a solution of bis-TBS ester 162 (0.027 g, 0.05 mmol) in THF (0.90 mL) at 0 °C was added TBAF (1M in THF, 50 µL, 0.05 mmol). The reaction was stirred for 1 hour at 0 °C, at which time an additional 1.0 equiv TBAF were added (50 µL). After stirring for 2 hours at 0 °C, the reaction was diluted with methylene chloride and quenched with sat. sodium bicarbonate. The layers were separated and the aqueous layer extracted 3x with methylene chloride. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10-30% EtOAc/Hex) to provide the product (0.0166 g, 76%) as a colorless oil. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 0.04 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 0.93 (d, J = 6.8 Hz, 3H), 1.20-1.34 (m, 4 H) 1.43 (s, 9H), 1.51-1.61 (m, 3H), 1.66 (s, 3H), 1.92-1.99 (m, 1H), 2.18 (t, J = 7.5 Hz, 2H), 2.36-2.42 (m, 1H), 2.85 (dd, J = 8.7, 2.6 Hz, 1H), 3.73-3.79 (m, 1H), 3.82-3.87 (m, 1H), 4.05 (s, 1H), 4.12-4.15 (m, 1H), 4.47 (dd, J = 10.9, 2.3 Hz, 1H), 5.36 (d, J = 9.4 Hz, 1H), 5.74 (dd, J = 10.2, 3.0 Hz, 1H), 5.91 (ddd, J = 10.2, 4.8, 1.9 Hz, 1H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 173.5, 133.4, 131.3, 129.7, 127.7, 80.0,
75.9, 73.7, 64.7, 62.2, 37.4, 35.8, 33.7, 32.0, 28.3, 27.1, 26.1, 25.4, 21.0, 18.4, 14.5, −3.9, −4.3; IR (film): 3434, 2928, 2857, 1731, 1646, 1462, 1391, 1366, 1253, 1154, 1113, 1065, 837, 775; ESI-MS: C_{27}H_{50}O_{5}Si [M+Na] calc. 505.33, found 505.3; [α]^{23}_{D} = 85.8° (c =0.09, CH_{2}Cl_{2}).

**Thioether 298:**

To a solution of alcohol 297 (0.025 g, 0.05 mmol), triphenylphosphine (0.027 g, 0.10 mmol) and 1-phenyl-1H-tetrazole-5-thiol (0.037 g, 0.21 mmol) in THF (1.0 mL) was added diisopropylazodicarboxylate (DIAD, 40 μL, 0.21 mmol). The reaction was stirred for 12 h at room temperature and then concentrated under reduced pressure. The crude product was purified by flash column chromatography (5-10% EtOAc/Hex) to provide the product (0.029 g, 87%) as a pale yellow oil. ^{1}H NMR (600 MHz, CDCl_{3}) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 0.92 (d, J = 6.8 Hz, 3H), 1.17-1.32 (m, 4H) 1.43 (s, 9H), 1.49-1.57 (m, 2H), 1.66 (s, 3H), 2.01-2.12 (m, 2H), 2.16 (t, J = 7.5 Hz, 4H), 2.35-2.41 (m, 1H), 3.40 (ddd, J = 13.2, 7.9, 7.9 Hz, 1H) 3.53 (ddd, J = 13.2, 7.9, 4.9 Hz, 1H), 4.01 (br. s., 1H), 4.12 (t, J = 3.6 Hz, 1H), 4.36-4.40 (m, 1H), 5.36 (d, J = 9.4 Hz, 1H), 5.74 (dd, J = 10.2, 2.6 Hz, 1H), 5.90 (ddd, J = 10.2, 4.5, 1.9 Hz, 1H), 7.49-7.62 (m, 5H); ^{13}C NMR (150 MHz, CDCl_{3}): δ 173.4, 154.6, 133.9, 133.5, 130.7, 130.3, 130.0, 129.8, 128.5, 124.0, 80.1, 76.4, 70.7, 65.3, 37.4, 35.8, 32.0, 31.9, 30.1, 28.3, 27.2, 26.1, 25.5, 21.0, 18.4, 14.4, −3.9, −4.3; IR (film): 2956, 2928, 2856, 1728, 1598, 1500, 1110, 837; ESI-MS: C_{34}H_{54}N_{4}O_{3}SSi [M+H] calc. 643.36, found 643.3; [α]^{23}_{D} = 65.2° (c =0.14, CH_{2}Cl_{2}).

![Diagram of thioether 298]
Sulfone 132:

To a solution of thioether 298 (0.025 g, 0.04 mmol) in EtOH (4 mL) at 0 °C was added a pre-mixed solution of (NH₄)₆Mo₇O₂₄•4H₂O (0.012 g, 0.01 mmol) in H₂O (30% aq, 60 µL, 0.58 mmol) via a glass pipette. The resulting yellow solution was allowed to warm to room temperature and stirred for 12 hours. The reaction was diluted with diethyl ether and quenched with sat. sodium bicarbonate and water. The layers were separated and the aqueous layer extracted 3x with diethyl ether. The combined organic layers were washed with sat. sodium sulfite, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5% EtOAc/Hex) to provide the product (0.021 g, 78%) as a pale yellow oil. ¹H NMR (600 MHz, CDCl₃) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 0.93 (d, J= 6.8 Hz, 3H), 1.18-1.35 (m, 4H), 1.43 (s, 9H), 1.51-1.56 (m, 2H), 1.68 (s, 3H), 2.09-2.18 (m, 3H), 2.21-2.27 (m, 1H), 2.35-2.44 (m, 1H), 3.79 (ddd, J= 15.4, 11.1, 5.1 Hz, 1H), 3.92 (ddd, J= 15.0, 11.0, 4.5 Hz, 1H), 4.05 (d, J= 2.6 Hz, 1H), 4.17 (t, J= 3.8 Hz, 1H), 4.29-4.34 (m, 1H), 5.39 (d, J= 9.4 Hz, 1H), 5.70 (dd, J= 10.2, 2.1 Hz, 1 H), 5.94 (ddd, J= 10.2, 4.2, 2.3 Hz, 1H), 7.58-7.63 (m, 3H), 7.68-7.70 (m, 2H); ¹³C NMR (150 MHz, CDCl₃): δ 173.4, 153.6, 134.4, 133.2, 131.6, 129.9, 129.8, 129.3, 129.1, 125.3, 80.0, 76.7, 69.8, 65.2, 53.4, 37.4, 35.8, 32.1, 28.3, 27.2, 26.0, 25.8, 25.4, 21.0, 18.3, 14.4, −4.1, −4.4; IR (film): 2928, 2857, 1728, 1462, 1340, 1252, 1156, 1111, 838, 775; ESI-MS: C₃₄H₅₄N₄O₆SSi [M+Na] calc.697.34, found 697.3; [α]D²¹ = 77.5° (c = 1.2, CH₂Cl₂).
To a dry 10 mL round bottom flask was added vinyl addition product 286 (0.064 g, 0.070 mmol) and 0.7 mL THF. The reaction mixture was cooled to 0 °C, and tetrabutylammonium fluoride (1M in THF, 0.70 mL, 0.70 mmol) was added dropwise. Upon completion of addition, the reaction was allowed to come to room temperature. After 12 hours stirring, additional tetrabutylammonium fluoride (0.35 mL, 0.35 mmol) was added and the reaction was stirred for another 12 hours. The reaction was diluted with CH₂Cl₂ and quenched with water. The aqueous layer was extracted 3x with CH₂Cl₂, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (100% EA to 50% acetone/EA) to give the product (0.030 g, 75%) as a white solid. ¹H NMR (600 MHz, CDCl₃) δ 0.84 (d, J= 6.4 Hz, 3H), 0.89 (d, J= 7.2 Hz, 3H), 1.34-1.43 (m, 1H), 1.57-1.63 (m, 1H), 1.63-1.71 (m, 2H), 1.71-1.81 (m, 2H), 1.84 (d, J= 11.3 Hz, 1H), 1.96-2.02 (m, 1H), 2.02-2.09 (m, 1H), 2.13-2.23 (m, 2H), 2.23-2.36 (m, 1H), 2.59 (br. s, 1 H), 3.16 (br. s., 1 H), 3.48 (t, J= 6.4 Hz, 1H), 3.65 (t, J= 5.8 Hz, 2H), 3.71-3.85 (m, 4H), 3.80 (s, 3H), 3.90-3.97 (m, 2H), 4.06-4.09 (m, 1H), 4.20 (t, J= 6.4 Hz, 1H), 4.24 (d, J= 6.4 Hz, 1H), 4.35 (br. s., 1H), 4.54 (q, J= 10.9 Hz, 2H), 5.44 (dd, J= 15.1, 7.5 Hz, 1H), 5.52-5.61 (m, 2H), 5.76-5.83 (m, 1H), 6.87 (d, J= 8.7 Hz, 2H), 7.29 (d, J= 8.7 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃): δ 159.3, 134.6, 132.3, 130.5, 130.2, 129.6, 129.2, 114.0, 81.9, 79.7, 79.0, 75.5, 75.0, 74.65, 74.63, 74.2, 73.0, 70.3, 67.8, 62.5, 55.5, 41.7, 38.9, 37.7, 35.7, 31.9, 30.5, 29.5, 15.4,
10.8; IR (film): 3418, 2958, 2933, 2871, 1613, 1513, 1376, 11248, 1074; ESI-MS: C$_{32}$H$_{48}$O$_9$ [M+Na] calc. 599.32, found 599.31; $[\alpha]_{D}^{25}$ = -19.8° (c = 0.25, CH$_2$Cl$_2$).

Acetonide 300:

To tetraol 299 (0.020 g, 0.035 mmol) in 1.0 mL dimethoxypropane in a dry vial under argon was added camphorsulfonic acid (1.0 mg, 0.003 mmol) at room temperature. After 12 hours stirring, the reaction mixture was diluted with CH$_2$Cl$_2$ and 10% HCl and stirred for 10 minutes. The layers were separated and the aqueous layer was extracted three times with CH$_2$Cl$_2$, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (100% EA) to give the product (0.020 g, 95%) as a colorless oil. $^1$H NMR (600 MHz, CDCl$_3$) δ 0.84 (d, J= 6.8 Hz, 3H), 0.90 (d, J= 7.2 Hz, 3H), 1.35 (s, 3H), 1.36-1.43 (m, 2H), 1.46 (s, 3H), 1.64-1.69 (m, 2H), 1.69-1.71 (m, 1H), 1.71-1.77 (m, 1H), 1.78 (br. s., 1H), 1.84 (d, J= 12.8 Hz, 1H), 2.00 (dd, J= 11.4, 6.7, 2.3 Hz, 1H), 2.07-2.14 (m, 1H), 2.18 (q, J= 7.2 Hz, 2H), 2.23-2.30 (m, 1H), 3.62-3.66 (m, 2H), 3.72-3.85 (m, 5H), 3.81 (s, 3H), 3.94-4.02 (m, 2H), 4.08 (td, J= 5.7, 1.9 Hz, 1H), 4.24 (d, J= 6.8 Hz, 1H), 4.35 (br. s., 1H), 4.54 (q, J= 11.7 Hz, 2H), 4.65 (t, J= 6.8 Hz, 1H), 5.43 (dd, J= 15.3, 7.7 Hz, 1H), 5.53 (ddd, J= 13.9, 7.7, 6.2 Hz, 1H), 5.58 (dd, J= 15.3, 7.0 Hz, 1H), 5.73-5.80 (m, 1H), 6.88 (d, J= 8.7 Hz, 2H), 7.29 (d, J= 8.7 Hz, 2H); $^{13}$C NMR (150 MHz, CDCl$_3$): δ 159.3, 133.5, 132.3, 130.5, 130.2, 129.6, 126.7, 114.0, 108.5, 81.8, 80.0, 79.7, 79.0, 78.7, 75.0, 73.5, 73.0, 71.2, 70.5, 67.7, 62.2, 55.5, 41.7, 38.9, 37.6, 35.9, 32.2, 30.9, 28.9, 27.8,
TBS protected acetonide:

To acetonide 300 (0.020 g, 0.03 mmol) in a dry 1 dram vial under argon was added imidazole (0.005 g, 0.06 mmol) and TBSCl (0.005 g, 0.06 mmol) successively. The reaction was stirred for 12 hours at room temperature, then quenched with sat. sodium bicarbonate. The aqueous layer was extracted three times with CH₂Cl₂, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (30-50% EA/Hex) to give the product (0.017 g, 72%) as a colorless oil. ¹H NMR (600 MHz, CDCl₃) δ 0.05 (s, 6H), 0.83 (d, J = 6.4 Hz, 3H), 0.86-0.94 (m, 12H), 1.35 (s, 3H), 1.35-1.41 (m, 1H), 1.45 (s, 3H), 1.54-1.65 (m, 2H), 1.66-1.77 (m, 2H), 1.84 (d, J = 10.9 Hz, 1H), 2.00 (ddd, J = 11.4, 6.7, 2.3 Hz, 1H), 2.07-2.17 (m, 4H), 2.24-2.31 (m, 1H), 3.62 (t, J = 6.4 Hz, 2H), 3.74 (t, J = 8.7 Hz, 1H), 3.76-3.86 (m, 4H), 3.80 (s, 3H), 3.92-3.99 (m, 2H), 4.05-4.10 (m, 1H), 4.24 (d, J = 6.8 Hz, 1H), 4.35 (br. s., 1H), 4.54 (q, J = 12.0 Hz, 2H), 4.63 (t, J = 7.0 Hz, 1H), 5.43 (dd, J = 15.4, 7.5 Hz, 1 H), 5.50 (dd, J = 8.5, 5.8 Hz, 1H), 5.54 (dd, J = 15.4, 7.5 Hz, 1H), 5.75-5.83 (m, 1H), 6.87 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃): δ 159.3, 134.1, 132.4, 130.6, 129.8, 129.6, 126.0, 114.0, 108.5, 81.9, 80.0, 79.6, 78.99, 78.95, 75.0, 73.2, 73.1, 71.2, 70.5, 67.9, 62.8, 55.5, 41.8, 38.9, 37.3, 35.8, 32.5, 31.2, 29.0, 27.9, 26.2, 25.6, 18.5, 15.5, 10.7, –5.0; IR (film): 3445, 2931, 1613, 1514, 1378, 1248,
1065, 836, 775; ESI-MS: C_{41}H_{66}O_{9}Si [M+Na] calc. 797.46, found 797.44; [α]^{20}_D = -22.7° (c = 0.23, CH_2Cl_2).

![Methoxy methyl ether 301](image)

**Methoxy methyl ether 301:**

To a dry round bottom flask was added the secondary alcohol (0.023 g, 0.031 mmol) in 0.8 mL CH_2Cl_2. Dimethylaminopyridine (1 equiv), sodium iodide (1 equiv) and di-iso-propylethyl amine (0.28 mL, 1.6 mmol) were added successively. The reaction mixture was cooled to 0 °C at which time methoxymethyl chloride (60 µL, 0.79 mmol) was added dropwise. The reaction mixture was allowed to come to room temperature and stirred for 12 hours. The reaction was quenched with sat. ammonium chloride and diluted with ethyl acetate. The aqueous layer was extracted twice with ethyl acetate, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (25% EA/Hex) to give the product (0.022 g, 85%) as a colorless oil. ^1H NMR (600 MHz, CDCl_3) δ 0.04 (s, 6H), 0.84 (d, J= 6.8 Hz, 3H), 0.87-0.93 (m, 12H), 1.35 (s, 3H), 1.35-1.41 (m, 1H), 1.45 (s, 3H), 1.59-1.67 (m, 3H), 1.70 (d, J= 7.2 Hz, 1H), 1.77 (d, J= 14.3 Hz, 1H), 1.84 (d, J= 11.3 Hz, 1H), 1.99 (ddd, J= 11.3, 6.8, 2.3 Hz, 1H), 2.06-2.16 (m, 3H), 2.23-2.29 (m, 1H), 3.35 (s, 3H), 3.62 (t, J= 6.4 Hz, 2H), 3.71-3.84 (m, 6H), 3.80 (s, 3H), 3.95 (t, J= 7.0 Hz, 1H), 4.07 (t, J= 4.9 Hz, 1H), 4.24 (d, J= 6.4 Hz, 1H), 4.35 (br. s., 1H), 4.50 (d, J= 11.7 Hz, 1H), 4.55 (d, J= 11.3 Hz, 1H), 4.63 (t, J= 6.8 Hz, 1H), 4.66 (q, J= 6.8 Hz, 2H), 5.43 (dd, J= 15.3, 7.7 Hz, 1H), 5.50-
5.58 (m, 2H), 5.75-5.83 (m, 1H), 6.87 (d, J= 8.3 Hz, 2H), 7.28 (d, J= 8.3 Hz, 2H); $^{13}$C NMR (150 MHz, CDCl$_3$): δ 159.4, 134.2, 132.4, 129.9, 129.6, 126.0, 113.9, 108.4, 95.0, 82.0, 80.1, 79.7, 79.0, 78.9, 75.4, 75.0, 73.8, 73.1, 71.8, 68.0, 62.8, 55.6, 55.5, 41.8, 38.9, 35.9, 35.1, 32.5, 29.0, 28.7, 27.8, 26.2, 25.6, 18.5, 15.4, 10.8, −5.1; IR (film): 2931, 1642, 1514, 1248, 1099, 1038, 836; ESI-MS: C$_{43}$H$_{70}$O$_{10}$Si [M+Na] calc. 797.46, found 797.4; $[^{23}]$D = −14.3° (c = 0.35, CH$_2$Cl$_2$).

**Alcohol 302:** To a dry 10 mL round bottom flask containing p-methoxybenzyl ether 301 (0.019 g, 0.025 mmol) was added 1.2 mL CH$_2$Cl$_2$ and 60 μL pH 7 buffer. The solution was cooled to 0 °C, and DDQ (0.009 g, 0.038 mmol) was added in one portion. After 1 hour at 0 °C, a second portion of DDQ (0.009 g, 0.038 mmol) was added. The reaction was stirred an additional hour then diluted with CH$_2$Cl$_2$ and quenched with sat. sodium bicarbonate. The aqueous layer was extracted 3x with CH$_2$Cl$_2$, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (25-50% EA/Hex) to give the product (0.014 g, 84%) as a light yellow oil. $^1$H NMR (600 MHz, CDCl$_3$) δ 0.05 (s, 6H), 0.85 (d, J= 6.4 Hz, 3H), 0.87-0.92 (m, 12H), 1.34 (s, 3H), 1.37-1.43 (m, 1H), 1.44 (s, 3H), 1.58-1.71 (m, 4H), 1.77 (d, J= 13.9 Hz, 1H), 1.86 (d, J= 11.3 Hz, 1H), 1.99-2.11 (m, 2H), 2.13 (q, J= 7.2 Hz, 2H), 2.21-2.28 (m, 1H), 3.35 (s, 3H), 3.64 (t, J= 6.2 Hz, 2H), 3.70-3.77 (m, 3H), 3.82-3.91 (m, 2H), 3.93 (t, J= 7.0 Hz, 1H), 3.96-4.05 (m, 2H), 4.27 (d, J= 6.4 Hz, 1H), 4.36 (br. s., 1H),
4.62 (t, \( J = 6.8 \) Hz, 1H), 4.66 (q, \( J = 7.2 \) Hz, 2H), 5.42 (dd, \( J = 15.3, 7.7 \) Hz, 1H), 5.50-5.63 (m, 2H), 5.75-5.83 (m, 1H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \( \delta \) 134.3, 132.2, 130.6, 125.8, 108.4, 94.8, 83.0, 80.0, 79.8, 79.0, 78.9, 75.2, 74.5, 73.2, 71.6, 62.9, 61.0, 55.6, 41.6, 39.0, 36.0, 35.3, 32.5, 29.0, 28.6, 27.9, 26.1, 25.6, 18.5, 15.4, 10.8, -5.1; IR (film): 3457, 2958, 2931, 1462, 1380, 1274, 1100, 1071, 837; \([\alpha]_{D}^{23} = -9.3^\circ (c = 0.18, CH_2Cl_2)\).

**Aldehyde 303:**

To alcohol 302 (0.029 g, 0.044 mmol) in 2.20 mL CH\(_2\)Cl\(_2\) was added Dess-Martin periodinane (0.038 g, 0.089 mmol) at room temperature. After stirring for 30 minutes, the reaction was quenched with 5:1 Na\(_2\)S\(_2\)O\(_3\): NaHCO\(_3\) and diluted with CH\(_2\)Cl\(_2\). The aqueous layer was extracted 3x with CH\(_2\)Cl\(_2\), dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (30-40% EA/Hex) to give the product (0.024 g, 83%) as a colorless oil, which was used immediately in the next reaction. \(^{1}\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 0.05 (s, 6H), 0.86-0.92 (m, 12H), 0.95 (d, \( J = 6.8 \) Hz, 3H), 1.34 (s, 3H), 1.44 (s, 3H), 1.45-1.51 (m, 2H), 1.58-1.65 (m, 3H), 1.66-1.71 (m, 1H), 1.76 (d, \( J = 14.3 \) Hz, 1H), 1.95-2.02 (m, 2H), 2.06-2.15 (m, 3H), 2.20-2.27 (m, 1H), 3.35 (s, 3H), 3.48 (t, \( J = 8.5 \) Hz, 1H), 3.63 (t, \( J = 6.4 \) Hz, 2H), 3.70-3.78 (m, 3H), 3.94 (t, \( J = 7.0 \) Hz, 1H), 4.37-4.42 (m, 2H), 4.62 (t, \( J = 6.8 \) Hz, 1H), 4.66 (q, \( J = 7.2 \) Hz, 2H), 4.81 (br. s., 1H), 5.41 (dd, \( J = 15.3, 7.3 \) Hz, 1H), 5.49-5.59 (m, 2H), 5.75-5.83 (m, 1H), 9.95 (s, 1H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \( \delta \) 198.6, 134.3,
E-vinyl iodide 172:

Chromium (II) chloride (0.056 g, 0.46 mmol) was heated with a heat gun under vacuum, then refilled with argon and allowed to cool to room temperature. Degassed THF (0.46 mL) was added to the flask, and the resulting suspension cooled to 0 °C and wrapped in aluminum foil and placed in the dark. Aldehyde 303 (0.030 g, 0.046 mmol) and iodoform (0.054 g, 0.14 mmol) in 1.40 mL dioxane were added by syringe pump over 1 hour, the flask was rinsed with dioxane (2 x 0.20 mL) to ensure complete transfer of the aldehyde. The reaction was allowed to come to room temperature and stirred for 12 hours at which time the suspension was quenched with brine and diluted with diethyl ether. The aqueous layer was extracted 3x with diethyl ether, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (hex-15-30% EA/Hex) to give E-vinyl iodide 172 (0.0144 g, 40%) and Z-vinyl iodide 304 (0.004 g, 11%) as pale yellow oils. ¹H NMR (600 MHz, C₆D₆) δ 0.09 (s, 6H), 0.79-0.83 (m, 6H), 1.00 (s, 9H), 1.05-1.10 (m, 1H), 1.32 (s, 3H), 1.39 (ddd, J= 11.7, 6.4, 2.6 Hz, 1H), 1.44 (d, J= 10.9 Hz, 1H), 1.51 (s, 3H), 1.60-1.76 (m, 4H), 2.00-2.08 (m, 2H), 2.22 (q, J=6.90 Hz, 2H), 2.35 (ddd, J= 13.9, 6.6, 6.6 Hz, 1H), 3.19 (s, 3H), 3.61 (t,
\( J = 6.4 \text{ Hz}, 2\text{H}, 3.66 \text{ (m, 1H), 3.82-3.85 (m, 1H), 3.87 \text{ (br. s., 1H), 3.91 (d, } J = 6.0 \text{ Hz, 1H), 3.97 (td, } J = 7.2, 1.9 \text{ Hz, 1H), 4.00 (dd, } J = 8.9, 7.7 \text{ Hz, 1H), 4.04-4.09 (m, 2H), 4.48-4.53 \text{ (m, 2H), 4.78 (t, } J = 5.7 \text{ Hz, 1H), 5.45 (dd, } J = 15.1, 7.2 \text{ Hz, 1H), 5.68 (ddd, } J = 14.7, 7.5, 7.5 \text{ Hz, 1H), 5.83 (dd, } J = 15.4, 6.4 \text{ Hz, 1H), 5.94 (ddd, } J = 15.4, 6.4, 6.4 \text{ Hz, 1H), 6.44 (dd, } J = 14.7, 1.5 \text{ Hz, 1H), 6.82 (dd, } J = 14.5, 4.7 \text{ Hz, 1H}); ^{13}\text{C NMR (150 MHz, C}_{6}\text{D}_{6}})\): \( \delta 142.0, 132.7, 132.6, 129.2, 127.5, 108.4, 95.1, 83.6, 80.6, 79.4, 79.2, 79.0, 78.6, 75.8, 75.5, 73.9, 72.0, 62.7, 55.2, 41.7, 38.7, 36.3, 35.6, 33.0, 29.6, 29.2, 28.2, 26.2, 25.7, 18.5, 15.2, 10.8, -5.1; IR (film): 2931, 2857, 1602, 1462, 1380, 1254, 1217, 1143, 1099, 1067, 1038; ESI-MS: C_{36}H_{61}IO_{8}Si [M+Na] \text{ calc. 799.31, found 799.28; } [\alpha]^{24}_{D} = -19.6^\circ \text{ (c = 0.72, C}_{6}\text{H}_{6}).\)

Alcohol 305:

To TBS ether 172 (0.0105 g, mmol) in 0.5 mL THF at \(-20^\circ\text{C}\) in the dark was added TBAF (1M in THF, 20 \(\mu\text{L}, \text{mmol}). \) After 30 minutes stirring, the reaction was warmed to room temperature and stirred an additional 2 hours, at which time additional TBAF (20 \(\mu\text{L})\) was added. The reaction was stirred an additional hour and diluted with saturated NaHCO\(_3\) (3 mL), water (10 mL) and EtOAc (15 mL). The aqueous layer was extracted 3x with ethyl acetate, and the combined organic layers were dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (50-70-100% EtOAc/Hex) to give the product (0.0085 g, 95%)
as a light yellow oil. $^1$H NMR (600 MHz, C$_6$D$_6$) $\delta$ 0.78-0.83 (m, 6H), 1.04-1.10 (m, 1H), 1.32 (s, 3H), 1.39 (ddd, $J$= 11.3, 6.6, 2.8 Hz, 1H), 1.46 (d, $J$= 11.3 Hz, 1H), 1.51 (s, 3H), 1.56-1.60 (m, 2H), 1.64-1.70 (m, 1H), 1.70-1.76 (m, 1H), 2.00-2.07 (m, 2H), 2.14 (q, $J$= 7.2 Hz, 2H), 2.32 (ddd, $J$= 14.1, 6.9, 6.9 Hz, 1H), 3.19 (s, 3H), 3.48 (t, $J$= 6.4 Hz, 2H), 3.63-3.66 (m, 1H), 3.79-3.82 (m, 1H), 3.87 (br. s, 1H), 3.89 (d, $J$= 6.4 Hz, 1H), 3.96 (ddd, $J$= 7.0, 7.0, 1.9 Hz, 1H), 4.01 (dd, $J$=9.0, 7.5 Hz, 1H), 4.04-4.10 (m, 2H), 4.50 (br. s., 2H), 4.77 (t, $J$= 5.7 Hz, 1H), 5.46 (dd, $J$= 15.1, 7.2 Hz, 1H), 5.70 (ddd, $J$= 14.7, 6.8, 6.8 Hz, 1H), 5.81 (dd, $J$= 15.4, 6.0 Hz, 1H), 5.85-5.93 (m, 1H), 6.43 (dd, $J$= 14.5, 1.7 Hz, 1H), 6.83 (dd, $J$= 14.3, 4.9 Hz, 1H); $^{13}$C NMR (150 MHz, C$_6$D$_6$) $\delta$ 141.9, 132.6, 132.4, 129.7, 127.6, 108.4, 95.2, 83.5, 80.5, 79.4, 79.2, 79.1, 78.7, 76.0, 75.5, 74.1, 72.0, 62.1, 55.3, 41.7, 38.7, 36.4, 35.7, 32.8, 29.6, 29.1, 28.1, 25.6, 15.2, 10.9; IR (film): 3458, 2931, 2870, 1671, 1603, 1456, 1380, 1217, 1144, 1098, 1066, 1037; ESI-MS: C$_{30}$H$_{47}$IO$_8$Si [M+Na] calc. 685.22, found 685.20; $[\alpha]^D_D = -29.8^\circ$ (c = 0.35, C$_6$H$_6$).

Aldehyde 173:

To alcohol 305 (0.007 g, 0.011 mmol) and sodium bicarbonate (0.011 g, 0.132 mmol) in 0.6 mL CH$_2$Cl$_2$ at room temperature was added Dess-Martin periodinane (0.013 g, 0.032 mmol). The reaction mixture was stirred for 2 hours, at which time 2 mL diethyl ether and 3 mL of 1:1:1 sat. NaCO$_3$/brine/Na$_2$S$_2$O$_3$ was added to the flask and stirred for 20 minutes until the aqueous layer became homogeneous. The layers were separated and
the aqueous layer extracted 3x with diethyl ether. The combined organic extracts were
dried over Na$_2$SO$_4$, filtered over a plug of silica gel (washing with ether), and
concentrated under reduced pressure. The crude product was purified by flash column
chromatography (50% EA/Hex) to deliver the product (0.005 g, 72%) as a colorless oil.
$^1$H NMR (600 MHz, C$_6$D$_6$) $\delta$ 0.76-0.83 (m, 6H), 1.04-1.10 (m, 1H), 1.30 (s, 3H), 1.36-1.46
(m, 3H), 1.50 (s, 3H), 1.60-1.69 (m, 1H), 1.70-1.76 (m, 1H), 1.96-2.06 (m, 4H), 2.18-2.25
(m, 1H), 2.27-2.33 (m, 1H), 3.19 (s, 3H), 3.63-3.67 (m, 1H), 3.80-3.83 (m, 1H), 3.86 (br.
s., 1H), 3.89 (d, $J$= 5.7 Hz, 1H), 3.95 (m, 1H), 3.98-4.06 (m, 3H), 4.52 (s, 2H), 4.71 (t, $J$=
5.8 Hz, 1H), 5.46 (dd, $J$= 15.3, 7.0 Hz, 1H), 5.70 (ddd, $J$= 14.9, 14.9, 7.9 Hz, 1H), 5.75
(d, $J$= 6.0 Hz, 1H), 5.80 (ddd, $J$= 13.6, 6.4, 6.4 Hz, 1H), 6.43 (dd, $J$= 14.5, 1.7 Hz, 1H),
6.80 (dd, $J$= 14.5, 4.7 Hz, 1 H), 9.37 (s, 1H); $^{13}$C NMR (150 MHz, C$_6$D$_6$): $\delta$ 200.3, 142.0,
132.6, 130.7, 129.2, 127.6, 108.4, 95.2, 83.6, 80.5, 79.4, 78.9, 78.8, 78.4, 75.7, 75.5,
73.9, 71.9, 55.2, 43.2, 41.8, 38.7, 36.4, 35.8, 29.7, 28.1, 25.6, 25.2, 15.2, 10.8.
C1-C38 fragment 174:

To a flame-dried 5 mL round bottom flask in the dark was added sulfone 132 (0.008 g, 0.012 mmol) and 0.12 mL DME. The solution was cooled to −78 °C, at which time KHMDS (0.5 M in toluene, 24 µL, mmol) was added dropwise via syringe. After stirring for 15 minutes, aldehyde 173 (0.004 g, 0.006 mmol) in 0.12 mL DME was added dropwise via syringe to the yellow solution. The reaction mixture was warmed to room temperature over 2 hours then diluted with ether and quenched with sat. NH₄Cl. The aqueous layer was extracted 3x with diethyl ether, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (5-30% EA/Hex, silica gel pretreated with 0.5% Et₃N) to give the product (0.0053 g, 79%) as a light yellow oil, along with 2.4 mg sulfone (58%). ¹H NMR (600 MHz, C₆D₆) δ 0.08 (s, 3H), 0.11 (s, 3H), 0.81 (d, J= 6.8 Hz, 3H), 0.82 (d, J= 7.2 Hz, 3H), 0.99 (s, 9H), 1.04 (d, J= 6.4 Hz, 3H), 1.06-1.10 (m, 1H), 1.23-1.31 (m, 4H), 1.33 (s, 3H), 1.41 (s, 9H), 1.43-1.51 (m, 2H), 1.53 (s, 3H), 1.61-1.69 (m, 3H), 1.69-1.76 (m, 1H), 1.83 (s, 3H), 1.99-2.06 (m, 2H), 2.14-2.27 (m, 7H), 2.30-2.37 (m, 1H), 2.39-2.45 (m, 2H), 3.20 (s, 3H), 3.65-3.69 (m, 1H), 3.83-3.86 (m, 1H), 3.89 (br. s., 1H), 3.92 (d, J= 6.0 Hz, 1H), 3.98 (ddd, J= 7.9, 7.9, 1.9 Hz, 1H), 4.01 (dd, J= 8.7, 7.9 Hz, 1H), 4.04-4.09 (m, 3H),
4.11 (br. s., 1H), 4.27 (t, $J = 7.2$ Hz, 1H), 4.52-4.55 (m, 2H), 4.79 (t, $J = 5.5$ Hz, 1H), 5.45 (dd, $J = 15.4$, 7.2 Hz, 1H), 5.49-5.59 (m, 3H), 5.70 (ddd, $J = 14.6$, 7.2, 7.2 Hz, 1H), 5.75 (dd, $J = 10.4$, 2.5 Hz, 1H), 5.82 (dd, $J = 14.7$, 6.4 Hz, 1H), 5.87 (ddd, $J = 10.2$, 4.7, 2.1 Hz, 1H), 5.92-5.99 (m, 1H), 6.45 (dd, $J = 14.7$, 1.5 Hz, 1H), 6.83 (dd, $J = 14.5$, 4.7 Hz, 1H); 

$^{13}$C NMR (150 MHz, C$_6$D$_6$): δ 172.5, 142.0, 133.1, 132.6, 132.5, 132.4, 132.1, 131.2, 129.5, 127.6, 127.0, 108.4, 95.1, 83.6, 80.6, 79.4, 79.3, 79.1, 79.0, 78.5, 76.7, 75.8, 75.5, 74.0, 72.7, 71.9, 66.0, 55.2, 41.8, 38.8, 37.8, 36.9, 36.4, 35.79, 35.76, 33.0, 32.9, 32.2, 29.6, 28.2, 27.5, 26.2, 25.74, 25.68, 21.3, 18.4, 15.2, 14.5, 10.8, −3.7, −4.2; IR (film): 2928, 2857, 1729, 1461, 1367, 1100, 1067, 1038, 837, 775; ESI-MS: C$_{57}$H$_{93}$IO$_{11}$Si [M+Na] calc. 1131.54, found 1131.50; $[\alpha]^{24}_D = +45.0^\circ$ ($c = 0.27$, C$_6$H$_6$).
$^1$H NMR SPECTRUM OF 263 (600 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 263 (150 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 264 (600 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 264 (150 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 278 (600 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 278 (150 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 281 (600 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 281 (150 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 282 (500 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 282 (150 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 286 (600 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 286 (150 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 293 (600 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 293 (150 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 294 (500 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 294 (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF THE DIOL (600 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF THE DIOL (150 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 295 (600 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 295 (150 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF THE ALCOHOL (600 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF THE ALCOHOL (150 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 296 (600 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 296 (150 MHz, CDCl$_3$)
$^1\text{H NMR SPECTRUM OF 162 (500 MHz, CDCl}_3\text{)}$
$^{13}$C NMR SPECTRUM OF **162** (125 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 297 (600 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 297 (150 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 298 (600 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 298 (150 MHz, CDCl$_3$)
$^1\text{H NMR SPECTRUM OF 132 (600 MHz, CDCl}_3\text{)}$
$^{13}$C NMR SPECTRUM OF 132 (150 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 299 (600 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 299 (150 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 300 (600 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 300 (150 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF THE TBS-PROTECTED ACETONIDE (600 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF THE TBS-PROTECTED ACETONIDE (150 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 301 (600 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 301 (150 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 302 (600 MHz, CDCl$_3$)
$^{13}$C NMR SPECTRUM OF 302 (150 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 303 (600 MHz, CDCl$_3$)
$	extsuperscript{13}$C NMR SPECTRUM OF 303 (150 MHz, CDCl$_3$)
$^1$H NMR SPECTRUM OF 172 (600 MHz, C$_6$D$_6$)
$^{13}$C NMR SPECTRUM OF 172 (150 MHz, C$_6$D$_6$)
$^1$H NMR SPECTRUM OF 305 (600 MHz, $C_6D_6$)
$^{13}$C NMR SPECTRUM OF 305 (150 MHz, C$_6$D$_6$)
$^1$H NMR SPECTRUM OF 173 (600 MHz, C$_6$D$_6$)
$^{13}$C NMR SPECTRUM OF 173 (150 MHz, C$_6$D$_6$)
$^1$H NMR SPECTRUM OF 174 (600 MHz, C$_6$D$_6$)
$^{13}$C NMR SPECTRUM OF 174 (150 MHz, C$_6$D$_6$)
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